Archives of Dermatology and Syphilology

VOLUME 57 FEBRUARY 1948 NUMBER 2

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MICROSCOPIC GRADING OF CANCER AND ITS PRACTICAL IMPLICATION

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A DISCUSSION of the microscopic grading of cancer [1] and its practical application will be made from the viewpoint of the practice of this procedure. A brief history [2] of the idea would be in order. Virchow in 1858 postulated that there were differences in malignancy of tumors in the matter only of degree. Hansemann spent many years studying the histology of cancer, beginning in 1890, elaborating on the earlier work of Pfitzner, Klebs and Arnold. The conclusions and observations of Hansemann form the basis on which Broders applied the grading of cancer to clinical work, announced [3] in 1920. However, Broders came to his conclusions independently [4] and many years after Hansemann's work was forgotten and relegated to the shelf of academic curiosity. Also, in 1912, Schottlander and Kermauner endeavored to apply Hansemann's principles, but failed to think them of clinical significance. Solomon, in 1913, in his studies of carcinomas of the breast, realized the importance of grading of cancer in prognosis.

The grading of malignancy is based, broadly, on the fact that among growths there is individuality, depending on the type of tissue from which the neoplasm has sprung, the site of growth, the type of its growth and, as is most important, the degree of differentiation and dedifferentiation (anaplasia) of the cells of the tumor. It is from this last concept that the weight of evidence for grading is drawn. The

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1. Cancer in this treatise will refer to squamous cell carcinoma and adenocarcinoma unless otherwise specified.

2. Broders, A. C.: Grading of Cancer, in Pack, G. T., and Livingston, E. M.: Treatment of Cancer and Allied Diseases, ed. 1, New York. Paul B. Hoeber, Inc., 1940, pp. 19-41.

3. Broders, A. C.: Squamous Cell Epithelioma of Lip: A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74**:656-664 (March 6) 1920.

4. Broders, A. C.: Conversations with Students of Pathology, the Mayo Clinic, July 1940, unpublished data.

other factors, except the "mother cell," being brought into account only secondarily. As Broders briefly stated,[2] malignant tissue is graded 1 if more than 75 per cent of the cells are differentiated, graded 2 if 50 per cent to 75 per cent are differentiated, graded 3 if 25 per cent to 50 per cent are differentiated and graded 4 if zero to 25 per cent are differentiated (or if 75 per cent to 100 per cent are dedifferentiated, i.e., anaplastic). This criterion may be applied to any neoplasm as to the grading of its malignancy cytologically. As can be realized immediately, the putting into practice of this criterion literally, necessitating the actual counting of cells, is impracticable, but the associated cytologic changes and morphologic characteristics of the tissue are more easily seen. Since these are direct results of the cellular activity, they furnish rather accurate evidences of malignant potentialities and their degree.

The interpretations of these cytologic and morphologic changes, as indicating degrees of anaplasia, of course, must be based on a large personal factor, but careful comparisons of numbers of sections, guided by the qualitative differences listed later as to cellular activity, will result in a more or less crystallized opinion as to various degrees of activity of the malignant process, which opinion will correspond closely to Broders' classification, if degrees of activity are divided into four classes.

This personal factor is a great objection in Jensen's opinion.[5] He felt that the grading of tumors is hazardous because of the liability of great error, of the wide differences of opinion regarding details of its application and of the variance of opinion of different pathologists concerning grade. He expressed the belief, also, that the attempt to express purely qualitative differences in terms of numerals is basically inaccurate. Bloodgood[6] emphasized the importance of having more than one pathologist render an opinion as to grading in order to lessen the danger of personal error. McDonald and Hueper[7] also felt that none of the various methods of grading were entirely free from the influence of personal equation and that results in grading generally are the results of group grading and not the result of the absolute grading in the individual case.

It has been argued that this method of grading is of little value because one field of a tissue section sometimes shows evidence of a different grade of malignancy than another field. This hardly seems a valid argument, because, in the first place, if one is observing a field in which there is evidence of malignancy, this is an uncommon observation.[2]

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5. Jensen, C. R.: Role of Biopsy in Diagnosis, Northwest Med. **36**:114-117, 1937.

6. Bloodgood, J. C.: Biopsy in Diagnosis of Malignancy, South. M. J. **20**: 18-28, 1927.

7. McDonald, E., and Hueper, W. C.: Cancer and the Laboratory, J. Lab. & Clin. Med. **16**:713-733, 1931.

Second, this observation does not alter the criteria of grading. Third, grading is not made on observation of one field of tissue or, for that matter, on one section of the tissue in question.

However, there are many borderline sections which are difficult to grade because of the merging of one grade into another. In these cases different pathologists, or the same one, may grade a growth differently on different occasions. Of course, the personal element cannot be eliminated, but it should be a general rule, as Broders [8] suggested, to err rather on the side of the higher grade, because malignant processes tend to be progressive rather than regressive. "Potency of undifferentiated cells is relatively greater; when determination has occurred, they cannot turn back."[9] Also, it has been noted in a small number of cases that metastases of a growth may show a different grade of malignancy than that of the parent growth. This phenomenon had been noted by Hansemann.[2] This difference, however, is almost inevitably that of an increase in dedifferentiation of cells in the metastasis, placing it in the next higher grade.[2] This also substantiates the proposition of grading the borderline tissues on the side of the higher grade of malignancy.

Cathie [10] graded 67 cases of primary carcinoma histologically and compared the grading with the metastases. In 34 cases the grading of the primary and secondary growths was the same. In 31 cases the primary was less differentiated than the secondary growths, and in 2 cases the primary was more differentiated than its secondary deposits. He concluded that the grading of a tumor and its metastases had no constant relationship.

Also, the objection has appeared since the first publishing of this system that the number of mitoses present in the section is not a valid basis on which to grade the malignancy of a process. This Broders conceded.[11] It is to be remembered that the number of mitoses is not the basis of grading, but merely an adjuvant to aid the pathologist in his evaluation. Generally, it can be said that the number of mitoses and particularly the presence and number of pathologic mitotic figures (e.g., "Y" formations), as judged by the irregular number of chromosomes and their abnormal arrangement, suggest an active cellular process of higher malignancy.[4]

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8. Broders, A. C.: Lectures to Students of Pathology, the Mayo Clinic, July 1940, unpublished data.

9. Reimann, S.: Lectures in Oncology, Hahnemann Medical College, November 1940, unpublished data.

10. Cathie, I. A. B.: The Relative Grading of Primary and Secondary Carcinoma, Brit. J. Radiol. **22**:94-95, 1939.

11. Broders, A. C.: Cancer's Self-Control, M. J. & Rec. **121**:133-135, 1925.

The application of grading of carcinomas depends on various histologic features and their degree of absence or presence. In squamous cell epitheliomas [11] the presence in the cells of keratinohyalinized or keratinized cytoplasm, eccentric or degenerated nucleoplasm, suggests differentiation. Pearly body formation and cornification suggest maturity of cells. Pigmentation is a sign of differentiation.[4] Dedifferentiated squamous cells will show no keratinization of cytoplasm; the cytoplasm will be smaller in volume in comparison with the nucleoplasm. The nucleoplasm will seem smaller in comparison to that of differentiated cells, will be spheroidal in shape and will be located in the center of the cytoplasm. No degeneration is likely. The nuclei of the cells will be more basophilic, and there will be more mitoses present and, perhaps, abnormal mitotic figures.

Partially differentiated adenocarcinomatous cells [11] will show spheroidal or spindle-shaped nuclei, which will usually be at the base of the columnar cell. The volume of the nucleus will be small compared with the cytoplasm. These cells may or may not have secretory products.[12] (Greenough, applying this method to mammary cancer, emphasized the signs of secretion and atypical qualities of the cells; signet ring carcinomas of the stomach usually are graded 3 or 4.[2]) As the nuclei become elongated and approach the apex of the cell, the cell shows more dedifferentiation. The nucleoli in malignant cells are larger in ratio to the nucleus than in nonmalignant cells.[13] The cells in forming the acini of glandular structure show differentiation, so that the more distorted the glandular arrangement or the further the migration of cells from the acinus, the more malignant are those cells.

The method or degree of invasion has little to do with the grading of malignancy, as can be seen, and the cytologic features are the most important criteria of the rate of growth and degree of differentiation. An appreciation of the cellular deviation from normal, that is, the extent of dedifferentiation, is THE criterion of grading.

According to Ewing [14] growth capacity and potential malignancy of tumors may be based on the following characteristics: (1) decided variation in the size of cells in either direction from the originating cells, (2) increase in chromatic nuclear substance, abundance, abnormality of mitoses and loss of polarity, (3) diffuse infiltrative growth of cells and (4) "perhaps" loss of reaction of the tissues against the infiltration of

12. Greenough, R. B.: Varying Degrees of Malignancy in Cancer of Breast, J. Cancer Research 9:453-463, 1925.

13. MacCarty, W. C.: Lectures to Students of Pathology, the Mayo Clinic, August 1940, unpublished data.

14. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 50.

tumor cells. General signs of increased nutrition and vitality of cells are emphasized.

An example of cytologic grading alone is the diagnosis of high grade malignancy by examination of ascitic fluid. Here, the presence of extremely few cells with multipolar mitotic figures is diagnostic of adenocarcinoma and almost always of grade 3 or 4.[4]

Martin and Stewart [15] have reported that they observed that it is often possible by aspiration biopsy to indicate the type of tumor, or even granuloma, and to determine the comparative malignancy, provided that the pathologist possesses complete clinical data. Their aspirations were from the lungs, liver, spleen, prostate, orbital cavity and neck, among other locations.

There are three main points on which the value of grading carcinomas rests. The first is that by statistical study of the grade of carcinomas in various locations more accurate diagnosis of the malignant tendency may be made clinically. The following list of average grades of malignant tissue in various locations was made by Broders.

Cases	Location	Average Grade *
537	Lip	2.07
256	Skin	2.19
473	Genitourinary region	2.92
362	Cavities, internal organs, head, neck	2.57
598	Rectum	2.23
3,368	Breast	3.30

* Average grade [2] equals the addition of aggregate grades divided by the number of cases graded.

Also, he listed the following average grades in consecutive cases of malignant growths that metastasized: [2]

Cases	Location	Average Grade
105	Lip	2.65
32	Skin	2.93
260	Rectum	2.46
2,495	Breast	3.52

The grades of malignant growths that did not metastasize in consecutive cases were:

Cases	Location	Average Grade
344	Lip	1.88
20	Skin	2.10
300	Rectum	2.12
873	Breast	2.67

It is obvious from these tables that carcinomas in certain locations tend to be more or less malignant than carcinomas in other locations and that carcinomas that metastasize generally are of higher grade

15. Martin, H. E., and Stewart, F. W.: Advantages and Limitations of Aspiration Biopsy, Am. J. Roentgenol. **35**:245-247, 1936.

than those that do not metastasize. These generalizations seem to me to have some clinical significance. Although cases should be individualized, it is logical to make limited presumptions on a statistical basis.

Concerning squamous cell epitheliomas,[2] those having high average malignancy are those of the tonsil, nasopharynx, posterior half of the tongue, esophagus, vagina and uterine cervix. Those tending to be of low average malignancy are those occurring on the anterior half of the tongue, buccal surface, cheeks, lips, skin, penis and labia. Adenocarcinomas[2] also tend to vary in their potentialities according to their location. Generally, highly malignant growths are, for example, adenocarcinomas of the breast and stomach, and of lower malignancy usually are adenocarcinomas of the large intestine, rectum and body of the uterus. These differences can hardly be explained by differences in blood and lymph supplies to the various locations. Obviously, that contention cannot apply to the high grade of malignancy of melanotic carcinoma of the skin and the low grade of malignancy of basal cell epithelioma of the skin, in which the basal cells seldom lose their characteristics and, if basal squamous epitheliomas are present, which constitute about 15 per cent of basal cell epitheliomas;[16] these are usually grade 2,[16] relatively low.

Carcinoma of the prostate is interesting from the viewpoint of grade of malignancy. Kahler[17] in a study of 195 cases made the following observations: In 6 cases of squamous cell carcinoma, 4 were graded 2 and 2 were graded 3. In 187 cases of adenocarcinoma, 19 per cent were graded 1, 50 per cent were graded 2, 27.5 per cent were graded 3 and 3.5 per cent were graded 4.

Kahler observed no evidence of relationship between the size of the cancer and the incidence of metastases.

One of the greatest values of the grading of carcinomas is its use as an aid in prognosis, before or after treatment has been instituted. As to surgical intervention, of course, the higher grade malignancies have a higher incidence of operative mortality, since generally a more extensive operation is used. However, after surgical treatment the prognosis is generally poorer for those who harbor a higher grade malignant growth. Whether this is due to already existent distant metastases or difficulty in removing the entire growth is a question depending on the particular case. Several surgeons of the Mayo Clinic[18] reported a series of cases

16. Montgomery, H.: Lecture to Students of Pathology, the Mayo Clinic, August 1940, unpublished data.

17. Kahler, J. E.: Carcinoma of the Prostate Gland, Proc. Staff Meet., Mayo Clin. **13**:589-592, 1938.

18. Walters, W.; Gray, H. K., and Priestley, J. T.: Malignant Lesions of the Stomach: Results of Treatment in the Years 1907-1938 Inclusive, S. Clin. North America **21**:1099-1115, 1941.

of carcinomas of the stomach in which resections were performed and in which the patients were still living and cured five years after resection.

Grade	Number Traced	Living Five Years	Percentage
1	29	25	86
2	190	110	59
3	136	95	30
4	270	62	23

Dixon and Imes [19] reported 145 cases of carcinoma of the cecum after resection; in 60 of these cases the patients were still living and cured five years after resection.

Grade	Number Traced	Grade	Number Traced
1	6	3	10
2	41	4	3

Harrington [20] reported a series of 1,691 consecutive cases of unilateral carcinoma of the breast, the average grade of which was 3.03, with the following results: 1,101 lived more than five years, average grade 2.93; 420 lived more than ten years, average grade 2.93; 1,598 failed to live more than three years, average grade 3.60; 1,867 failed to live more than five years, average grade 3.53, and 1,338 failed to live more than ten years, average grade 3.47.

Rankin and Broders [21] reported a series of 853 cases of carcinoma of the large bowel, with and without glandular involvement, in which the patients still were reported as cured after five years.

With glandular involvement (387 cases)				
Grade	1	2	3	4
Incidence	9%	51%	28%	12%
Still cured after 5 years	44%	34%	13%	15%
Without glandular involvement (466 cases)				
Grade	1	2	3	4
Incidence	16%	62%	16%	6%
Still cured after 5 years	69%	56%	49%	37%

Montgomery,[22] discussing the treatment of squamous cell epitheliomas of the lip, stated that as a general rule epitheliomas of grades 1 and 2 may be treated with excision and diathermy with good results (10 per cent recur, Broders [22]) and of grades 3 and 4 with poor prognosis after excision and radiation to the glands, because there are usually

19. Dixon, C. F., and Imes, P. R.: The Curability of Carcinoma of the Cecum, Proc. Staff Meet., Mayo Clin. **9**:419-421, 1934.

20. Harrington, S. W.: Unilateral and Bilateral Carcinoma of the Breast: Results Three, Five, Ten, Fifteen, Twenty Years After Treatment, Minnesota Med. **21**:1-8, 1938; cited by Broders.[2]

21. Rankin, F. W., and Broders, A. C.: Factors Influencing Prognosis in Carcinoma of Rectum, Surg., Gynec. & Obst. **40**:660-667, 1928.

22. Broders, cited by Montgomery H.: Neoplasms of Skin, in Christopher, F.: Textbook of Surgery, ed. 3, Philadelphia, W. B. Saunders Company, 1942, p. 127.

metastases (10 per cent successful, Broders [22]). In summary, it seems that a good prognosis is inversely proportional to the grade of the malignancy of the lesion, in spite of thorough and radical treatment.

As to further practical application of grading to clinical procedures, it is a definite aid in judging treatment. The most obvious example of grading in relation to treatment is the universal treatment of squamous cell carcinoma of the uterine cervix. This growth is usually graded 3 or 4, and, occasionally, 2. It is known that tumors of greater cellular activity are more radiosensitive than those of lower activity [23] (because of the greater number of cells undergoing mitoses being perhaps more radiosensitive in this stage). This knowledge applied to cervical cancer has increased the effectiveness of treatment by irradiation with radium after electrocoagulation of the visible portion.[24] In cancer of the bladder, fulguration is recommended in grades 1 and 2 and radium therapy in grades 3 and 4.[2] In general, it might be said that the higher the grade the more radical the surgical treatment indicated, if possible, and the less successful, conversely, the more effective is irradiation. In malignant growths of lower grade simple excision is likelier to be successful and the growth would be more radioresistant.

In my opinion the grading of carcinomas according to Broders' method is the best basis for classification of malignant tumors yet suggested for practical purposes in relation to clinical values. Also, the nomenclature pertaining to squamous cell carcinoma and adenocarcinoma, in particular, is far from standardized, and many surgeons believe it is an inadequate basis on which to prognosticate or to aid in judging treatment. (As Auchincloss observed [25] in relation to carcinoma of the breast, prognosis dependent on [pathologic] descriptive terms is not true.) These terms, descriptive as they supposedly are, vary so greatly among pathologists themselves that in the final analysis their value is just that much more reduced. Carcinomas should be graded according to the evidence of their activity, which would make for a greater unanimity of opinion and better clinical judgment and would, therefore, be of more accurate prognostic value. Of course, gross anatomy of the tumor, condition of lymph nodes, age and condition of the patient, duration of the disease, organs involved and heredity are to be considered as clinical features in the prognosis. The pathologic descriptive report of the tumor should be understood as descriptive only and not as a basis for activity of the lesion.

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23. Sappington, S.: Lectures in Pathology, Hahnemann Medical College, January 1939, unpublished data.

24. Danforth, W. C.: Tumors of Uterus, in Christopher, F.: Textbook of Surgery, ed. 3, Philadelphia, W. B. Saunders Company, 1942, p. 1519.

25. Auchincloss, H.: Tumors of Breast, in Christopher, F.: Textbook of Surgery, ed. 3, Philadelphia, W. B. Saunders Company, 1942, p. 903.

A listing of a few of the terms (MacCarty has listed 950 terms applied to neoplastic disease) that are used in describing carcinomas for surgeons are: (1) for squamous cell carcinomata—cutaneum, epidermoid, simplex, villosum, epithelioma, adenoid, cystic epithelioma, lympho-epithelioma, transitional cell carcinoma and acanthoma, plus various descriptive terms, as ulcerative, papillary and invasive, and (2) for adenocarcinomas—cylindric cell carcinoma, columnar cell, spheroidal cell, glandular, simplex, epitheliale adenoides, acinous, oat cell, adenomatosum, alveolar, colloid, hyaline, lenticulare, molle, muciparum, mucosum, myxomatodes, periportal, pultaceous, sarcomatodes, spongiosium, villosum, seminoma, hypernephroma (Grawitz tumor), malpighian, paramalpighian, polymorphic, fibrocarcinoma, scirrhous, medullary and encephaloid.

The purpose of this listing is to show the multiplicity of terms used, which are usually themselves elaborated on in the pathologic report. A much more informative and useful procedure would be naming the type of cancer, if possible, as squamous cell, basal cell and adenocarcinoma, and giving its grade. The pathologic description is of little use to the surgeon. Perhaps, though, a knowledge of the size of a tumor, method of growth, invasion and the like may be of interest in interpreting the history in a case and may be suggestive of a still more accurate prognosis, perused at the clinician's leisure.

Perhaps even the use of the words carcinoma, epithelioma and cancer is objectionable. In fact, perhaps practically the whole system of nomenclature of tumors should be revised to make for more understanding and accuracy.

MacCarty has suggested [26] a system that would seem to be an improvement over the present lack of system. He suggests that all neoplasms be classified using as a basis three great groups of tumors: (1) those neoplasms composed of adult cells, with normal arrangement of tissue, (2) those composed of cells normally or nearly normally arranged, but having a morphologic structure of malignant regenerative cells, and (3) those composed of cells of the malignant regenerative type not arranged in any fashion approaching that of any normal tissue. The nomenclature is based on the use of the basic suffixes,–cytoma and –blastoma, preceded by an identifying prefix, depending on the tissue cell of which the neoplasm is composed; for example, adenocytoma (benign glandular neoplasm) and adenoblastoma (malignant glandular neoplasm). Other prefixes suggested are chrondro–, epithelio–, endothelio–, fibro–, glio–, lipo–, lympho–, melano–, myxo–, neuro–, odonto–, osteo– or poly–. Problastoma is the word suggested for the neoplasms

26. MacCarty, W. C.: Importance of Nomenclature in Cancer Clinic, Surg., Gynec. & Obst. **54**:317-328, 1932.

of the class in which the cells of the tumor are completely dedifferentiated. For a combination of two types of cell, which may be present in one neoplasm, a combined word may be used, e.g., fibroadenoblastoma.

It is also suggested that there be a closer relationship between the surgical pathologist and the surgeon, especially as to operating room and pathologic laboratory diagnoses. Frozen sections should be made of all suspected malignant tissue and, if possible, the diagnosis and grade of malignancy established and returned to the surgeon immediately. This would lessen the errors of gross diagnosis and suggest the best treatment in a particular case.

SUMMARY

The practicability of grading malignant tissue according to Broders' classification as grades 1, 2, 3 and 4 as an indication of the degree of malignancy of the tissue graded is based on the following advantages: (1) A more accurate diagnosis of the malignant tendency of the growth may be made clinically by statistical study of the grades of carcinomas expected in various locations; (2) knowledge of the grade of malignancy is useful as an aid in prognosis in the case regardless of treatment, and (3) a more definite aid in therapeutic judgment is afforded.

The basis of grading malignant tissue is discussed, with emphasis on cytologic features aiding the pathologist in evaluating malignant potentialities.

Suggestions are made for a more uniform terminology of malignant tissue, with a summary of MacCarty's proposed system of nomenclature.

CUTANEOUS MANIFESTATIONS OF GONOCOCCIC INFECTION

Keratosis Blennorrhagica Treated with Penicillin

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THE GONOCOCCUS shows such affinity for the epithelium of the urogenital tract that it might easily be forgotten that not infrequently it is responsible for a variety of lesions at other sites. It is the purpose of this paper to emphasize one of the cutaneous lesions and to report a case in which treatment with penicillin was successful.

The cutaneous lesions due to infection with the gonococcus are generally divided into two groups. The first group of lesions is produced by invasion from without and includes intertriginous erythema, erosion, serpiginous ulceration, folliculitis and, rarely, tumor-like granuloma. In the second group a hematogenous mode of infection is postulated, and in this group are usually placed the exanthematous lesions and keratosis blennorrhagica (gonorrheal parakeratosis, gonorrheal keratosis).

Keratosis blennorrhagica was first described by Vidal [1] in 1885, and the syndrome of urethritis, cachexia, involvement of the joints and cutaneous eruption with involvement of nails and nail beds has since been noted in many publications. The lesions usually occur symmetrically on the trunk and extremities, especially on the palms and soles, in the form of layered cornified crusts. They begin as small inflamed papules, progressing to form cornified areas which when removed show a reddened, finely nodular, but nonweeping, base. While lesions on the face and trunk are small and discrete, on the feet and hands they coalesce to cover large areas.

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1. Vidal, E.: Eruption generalisée et symétrique de croûtes cornées, avec chute des ongles, d'origine blennorrhagique, coïncidant avec une polyarthrite de même nature: Récivide à la suite d'une nouvelle blenorrhagie, deux ans après la guérison de la première maladie, Ann. de dermat. et syph. 4:3, 1893.

The characteristics of this disease are best described by the following report of a typical case.

REPORT OF A CASE

Mr. E. B., a 41 year old single barber, was admitted on Aug. 7, 1945, complaining of an eruption of three weeks' duration and of tenderness and swelling of the left knee, of two weeks' duration. For some weeks he had noted burning on urination, frequency of urination and diminution in size and force of the urinary stream. He had also noted malaise, anorexia, loss of weight of 10 to 15 pounds (4.5 to 6.8 Kg.) and fever. The cutaneous lesions appeared three weeks before admission. These were painless and nonpruritic and had begun simultaneously at the hair line, on the scalp and at the groin. Later the eruption appeared in other areas, but was most evident on the buttocks and on the extremities. Two weeks before admission the left knee became tender, red, swollen and extremely painful with motion. The past history was relevant only in that he had had gonorrhea fifteen years previously, which was treated with urethral instillations and sounds. There was no recent history of reinfection nor any precipitating cause for the exacerbation. No history of allergy was elicited. The family history was noncontributory.

Physical Examination.—The following observations were made: temperature 99.2 F., pulse 78, respirations 20 and blood pressure 148 systolic and 84 diastolic. The patient appeared to be a slim well developed and well nourished man in no acute distress.

Skin: There were many erythematous exfoliative plaques on the scalp. Scattered over the body, with a predilection for the buttocks, thighs, feet and ankles, were many erythematous exfoliative areas, varying in size from 1 mm. to several centimeters in diameter. Many of the lesions on the legs and feet were raised and shaped like an inverted cone, the skin around the base being grayish and scaly. These hard cones could easily be lifted off, leaving a slightly moist raised base. There were numerous whitish keratotic lesions on the soles and palms. There were lesions of this nature on the nail beds on about half the fingers and toes, and here the nails were loose and raised (fig. 1).

Genitals: There was moderate balanitis. There was no frank urethral discharge.

Rectal Area: The prostate showed moderate diffuse enlargement. It was smooth, soft and tender.

Skeletal Observations: The left knee was moderately swollen, red, hot and tender on pressure, with decided limitation of motion due to pain.

Laboratory Observations.—Urinalysis revealed a specific gravity of 1.012, an acid reaction, a trace of albumin, negative results in the test for glucose, 40 to 45 leukocytes and 125 to 150 erythrocytes (high power field after centrifugation). The hemoglobin was 11.8 Gm. per hundred cubic centimeters, red blood cell count 3,850,000 per cubic millimeter and white blood cell count 18,200 per cubic millimeter, with a differential count of neutrophils 86 per cent, eosinophils 1 per cent, lymphocytes 12 per cent and monocytes 1 per cent. Studies of the chemical content of the blood showed urea nitrogen 45 mg. and glucose 98 mg. per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood were negative. Dark field examinations of several of the cutaneous lesions were negative for spirochetes. Smears from prostatic secretion following massage were repeatedly positive for gram-negative intracellular diplococci. Cul-

tures were positive for Neisseria gonorrhoeae. All cultures of the blood were negative. Smears and cultures from fluid aspirated from the left knee were negative.

The electrocardiogram showed occasional ventricular extrasystoles. A roentgenogram of the chest on admission revealed no abnormalities, and a roentgenogram of the knee showed only soft tissue swelling. Biopsy specimens were taken from two of the cutaneous lesions on the legs under local anesthesia two days after admission.

Pathologic Report.—Gross Examination: Two ellipsoids of skin, 1.5 by 1 cm. each, were submitted for examination. In the center of one was a raised conical nodule with a crater-like center and a brown base. The second specimen consisted of a smaller and flatter nodule having the same appearance except for the lack of a central crater. On section both showed decidedly thickened gray-

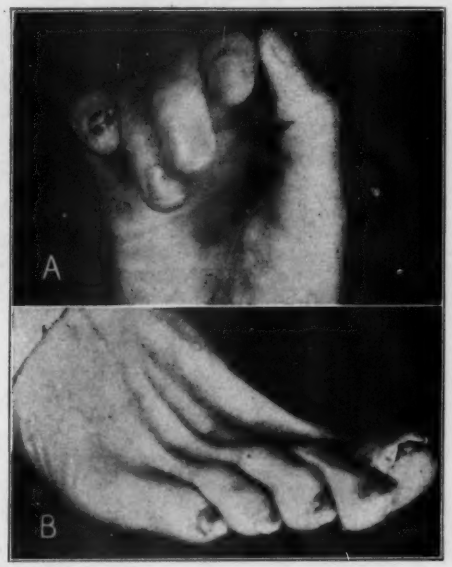

Fig. 1.—*A*, involvement of a finger nail. *B*, involvement of all the nails on one foot.

white epithelium with a sharply defined base. A small amount of yellowish brown soft material was contained in the smaller nodule.

Microscopic Examination: The sections were stained with hematoxylin and eosin, Goodpasture's modification of Gram's method and the Ziehl-Neelsen method.

Sections stained with hematoxylin and eosin showed a thick layer of surface parakeratosis. In the center of the nodule the parakeratotic layer was loose and edematous and showed infiltration with large numbers of polymorphonuclear leukocytes, lymphocytes and large mononuclear cells. The rete pegs were slightly hypertrophied and showed edema and an occasional infiltrating leukocyte. The upper portion of the corium was edematous and infiltrated with great numbers of acute and chronic inflammatory cells. Most of the inflammation appeared limited to the subpapillary layer (fig. 2 *A*). Numerous sweat glands were seen in the deep layer of the corium, and these showed a slight periglandular inflammatory reaction.

Sections stained by the Gram technic showed doubtful gram-negative diplococcic bodies in some of the leukocytes in the corium and in the parakeratotic layer. In the sweat glands there were numerous gram-negative intracellular diplococci, which were typically biscuit shaped (fig. 2*B*). Sections stained by the Ziehl-Neelsen technic failed to reveal the presence of acid-fast bacteria.

The diagnosis was keratosis blennorrhagica.

Treatment.—After the diagnosis was definitely established the patient was given 100,000 units of penicillin sodium intramuscularly over a period of twenty-five

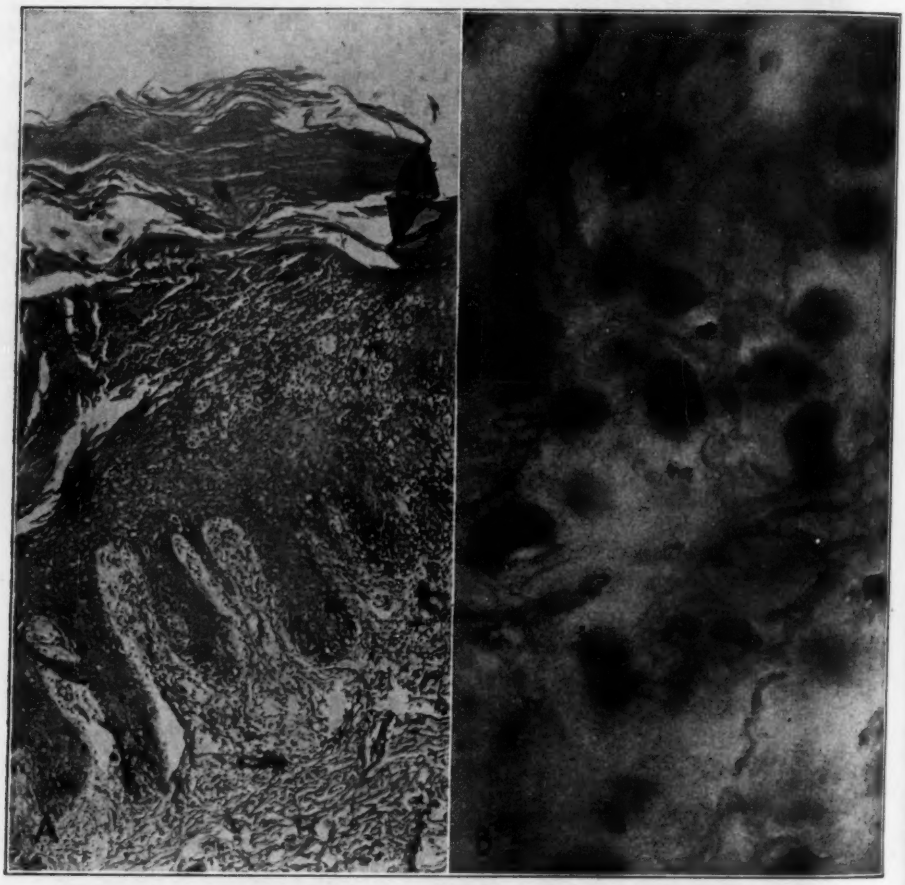

Fig. 2.—*A*, low power view of one of the lesions on the legs, showing parakeratosis, intraepidermal inflammatory reaction and the reaction in the papillary and subpapillary layers of the cutis (hematoxylin and eosin, × 60). *B*, sweat gland showing an intracellular gram-negative diplococcus (McCallum's gram stain, × 1500, oil immersion).

hours. Forty-eight hours later there seemed to be no improvement, and urethral smears still showed gram-negative intracellular diplococci. Penicillin therapy was therefore resumed, 10,000 units intramuscularly every four hours. By the time he had received a total of 2,200,000 units of penicillin the cutaneous lesions had entirely disappeared, as had the balanitis. The left knee joint was nontender,

and the prostate was normal on palpation. Repeated examinations of the prostatic secretions by smears and cultures yielded consistently negative results after 1,300,000 units of penicillin had been administered.

COMMENT

Keratosis blennorrhagica is not uncommon. By 1923 Buschke and Langer [2] had collected 58 cases, and including these we have found a total of 115 cases (plus 1 herein reported) in the literature up to the present time.

It is interesting to note that the incidence of keratosis blennorrhagica parallels the sex incidence of gonorrheal arthritis. It is therefore much more commonly seen in men. Of the 58 cases collected by Buschke and Langer,[2] only 5 occurred in women. Arning and Meyer-Delius [3] observed that in 4,300 cases of gonorrhea in men there were 147 cases of gonorrheal arthritis and 6 cases of keratosis blennorrhagica, while in 550 cases of gonorrhea in women there were only 12 cases of arthritis and no cases of keratosis.

As in gonorrheal arthritis, the organisms are not easily demonstrated or cultured. Of the 115 cases, besides ours, of keratosis blennorrhagica, gram-negative diplococci were demonstrated in tissue sections in 6 cases (Löhe,[4] Lees and Ferguson,[5] Wadsack,[6] Campbell,[7] DuBois [8] and Gager [9]) while in 5 cases intracellular gram-negative diplococci were demonstrated on direct smears from the cutaneous lesions (Hodara,[10] Scholtz,[11] Cole and Driver,[12] Berardi [13] and Barrett[13a]). Attempts to

2. Buschke, A., and Langer, E.: Hyperkeratotische Exantheme bei Gonorrhoe und ihre Beziehungen zur Psoriasis, Dermat. Wchnschr. **76**:145, 1923.

3. Arning, E., and Meyer-Delius, H.: Beitrag zur Klinik der gonorrhoischen Hyperkeratosis, Arch. f. Dermat. u. Syph. **108**:3, 1911.

4. Löhe, H.: Ueber einen Fall von herpetiformen gonorrhoischen Exanthem, Dermat. Ztschr. **15**:475, 1908.

5. Lees, F. S., and Ferguson, G. A.: Keratodermia Blenorrhagica: Some Further Observations as to Etiology, Brit. J. Dermat. **55**:125, 1943.

6. Wadsack, E.: Ein gonorrhoisches Exanthem, Berl. klin. Wchnschr. **43**:966, 1906.

7. Campbell, cited by Sutton, R. L.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1923, p. 438.

8. DuBois, cited by Hansteen, E. H.: Keratodermia Blennorrhagica, Internat. Clin. **4**:64, 1927.

9. Gager, E. C.: Keratoderma Blennorrhagica, J. A. M. A. **78**:941 (April 1) 1922.

10. Hodara, M.: Ein Fall von Gonokokkämie und generalisiertem gonorrhoischen Exanthem, Dermat. Wchnschr. **55**:397, 1912.

11. Scholtz, W.: Beiträge zur Biologie des Gonococcus, Arch. f. Dermat. u. Syph. **49**:1, 1899.

(Footnotes continued on next page)

culture the organisms have met with almost uniform failure. Margolin [14] being the only one able to culture N. gonorrhoeae from a cutaneous lesion.

Whether our case is worthy of inclusion in this group of cases in which organisms were demonstrated is uncertain. Gram-negative diplococcus-like structures were seen in some of the polymorphonuclear leukocytes making up the intradermal exudate, and typical gram-negative diplococci were not difficult to see within sweat gland cells. We believe that this observation should be interpreted with great caution, since our attempts to culture the organisms from biopsy tissue were unsuccessful and because of the numerous artefacts possible in such drastic handling of cells as occurs during fixation and staining. Nevertheless, the clinical picture is so typical and the histologic changes in the skin so characteristic that the diagnosis is not in doubt.

Were it not for the striking parallel between the evidence of dermatologic complications and gonorrheal arthritis one might question whether living organisms per se cause the cutaneous lesions. With such a high percentage of failure to conclusively demonstrate the organisms, raising the question of the lesion's being due to hypersensitivity to bacterial products seems warranted. Yet the positive demonstrations are not to be denied, and a similar situation obtains in demonstrating tubercle bacilli in the cutaneous lesions known or supposed to be tuberculous. The association with gonorrheal arthritis is suggestive, as is also the observation that in most of the cases reported there has been urethritis and/or prostatitis, and in over 50 per cent of these cases N. gonorrhoeae was cultured from urethral secretions. In 1 case (Hodara [10]) blood cultures taken at the time of the eruption were positive for N. gonorrhoeae.

The histologic structure of the lesions is as characteristic as the clinical picture. The earliest lesions begin in the midportion of the prickle cell layer with the formation of a vesicle which contains cellular debris and leukocytes. The cutis at this stage shows edema of the papillary and subpapillary layers, with early leukocytic infiltration. Later the vesicles change to pustules containing many leukocytes and covered by a layer of thick parakeratotic material. The rete pegs become elongated and thickened, and the inflammatory reaction of the cutis, although still limited to the papillary and subpapillary layers, is more evident. The oldest lesions are characterized by the thick layer of

12. Cole, H. N., and Driver, J. R.: Keratoderma Blennorrhagica, Arch. Dermat. & Syph. **19**:1025 (June) 1929.

13. Berardi, J. B.: Gonorrheal Keratosis: Report of a Case, Urol. & Cutan. Rev. **45**:768 (Dec.) 1941.

13a. Barrett, C. C.: Keratodermia Blemorrhagica, Arch. Dermat. & Syph. **22**: 627 (Oct.) 1930.

14. Margolin, E. S.: Gonorrheal Dermatitis as Part of Systemic Gonorrhea, Urol. & Cutan. Rev. **47**:512 (Sept.) 1943.

surface parakeratosis, with subsiding inflammatory changes in the epidermis and cutis.

We have been unable to find any reports of the treatment of keratosis blennorrhagica with penicillin. Our patient responded dramatically and completely to intensive treatment with penicillin.

SUMMARY

Keratosis blennorrhagica presents a typical clinical and histologic picture. A case is reviewed which showed a dramatic response to intensive penicillin therapy. Out of a total of 116 cases reported, organisms having the appearance of gonococci were observed in tissue sections in 11 cases, and in only 1 was the organism recovered on direct culture of the lesions. The significance of this is discussed.

ACANTHOSIS NIGRICANS AND ITS ASSOCIATION WITH CANCER

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NEW YORK

FIFTY per cent of cases of acanthosis nigricans, of which 420 cases have so far been reported,[1] are associated with internal cancer. Acanthosis nigricans provides an unexpected and helpful natural experiment for cancer research.

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1. For a summary of 395 cases up to 1943 see Curth, H. O.: Cancer Associated with Acanthosis Nigricans: Review of Literature and Report of a Case of Acanthosis Nigricans with Cancer of the Breast, Arch. Surg. **47**:517-552 (Dec.) 1943. Since then the following papers on the subject have been published or have become available: Frohn: Acanthosis nigricans (gutartige Form), Zentralbl. f. Haut- u. Geschlechtskr. **56**:232, 1937. Photinos, G.; Petropoulos, N.; Vossyniotis, C., and Karakiozides, J.: Acanthosis nigricans, ibid. **61**:617, 1939. Bruner: Acanthosis nigricans, ibid. **58**:609,1938. Gelli, G.: Considerazioni terapeutiche intorno a un caso di acanthosis nigricans, Pediatria prat. **10**:109, 1933. Zacharieff, B.: Acanthosis nigricans, Zentralbl. f. Haut- u. Geschlechtskr. **60**:292, 1938-1939. Wendelberger, J.: Acanthosis nigricans, Wien. klin. Wchnschr. **56**:551, 1943. Walker, J. J.: A Case for Diagnosis: Acanthosis Nigricans, Clin. Proc. **3**:239, 1944. Hollander, L.: Acanthosis Nigricans: Is It a Form of Avitaminosis? Arch. Dermat. & Syph. **48**:650 (Dec.) 1943. Jensen, A. K.: A Case for Diagnosis (Acanthosis Nigricans?), ibid. **54**:218 (Aug.) 1946. Wolf, J.: Acanthosis Nigricans (Juvenile), ibid. **54**:104 (July) 1946. Forman, L.: Acanthosis Nigricans with Discrete Warts and Marked Mucous Membrane Changes in a Patient with Vitiligo, Proc. Roy. Soc. Med. **36**:611, 1943. Peterkin, G. A. G., and Jones, E. C.: Clinical Notes on Two Cases of Acanthosis Nigricans, Brit. J. Dermat. **55**:185, 1943. Rothman, S., and Shapiro, A. L.: Acanthosis Nigricans, Juvenile Type, Arch. Dermat. & Syph. **52**:59 (July) 1945; Acanthosis Nigricans, Juvenile Type, ibid. **55**:139 (Jan.) 1947. Putman, F. L.: Acanthosis Nigricans, Juvenile Type, ibid. **51**:222 (March) 1945. Felsher, I. M., and Lieberthal, E. P.: Acanthosis Nigricans Juvenilis? ibid. **54**:620 (Nov.) 1946. Wise, F.: Acanthosis Nigricans, ibid. **41**:797 (April) 1940. Binkley, G. W., and Barr, J. H.: Acanthosis Nigricans, Benign Type with Acne and Active Duodenal Ulcer, ibid. **53**:69 (Jan.) 1946. Sullivan, M.: Acanthosis Nigricans, ibid. **34**:704 (Oct.) 1936. Warmoes, F., and Goubau, P.: Un cas d'acantosis nigricans en rélation avec un cancer de l'estomac, Acta gastro-enterol. belg. **9**:219, 1946. Gaté, M. J.: Acanthosis nigricans survenu un an après une hysterectomie pour néoplasme du col utérin, Ann. de dermat. et syph. **5**:336, 1945. Kaufman, W. H., and Smith, D. C.: Acanthosis Nigricans: A Case of the Benign Type in an Eight-Year Old Girl, Virginia M.

Strong[2] recommended the study of linkage to investigators of the origin of neoplastic tissue: "If one can demonstrate that the tendency to develop carcinoma is linked to (that is, carried on the same chromosome with) any hereditary color or morphological character, then one could prove that the new condition, i. e., the production of spontaneous carcinoma, is definitely inherited." In the problem confronting us my colleagues and I are dealing with human beings and not with experimental animals. Instead of hereditary color and morphologic character we are presented with discoloring and verrucous cutaneous disease which in a high percentage shows signs of genodermatosis, i. e. dermatosis originating from the germ plasm. The advantages and disadvantages of this situation for cancer research are obvious.

We profit by the fact that the cancer in question actually occurs in human beings. Observation of the two diseases and their relationship can be carried out longer in human beings than in experimental animals. Periods of observation could cover not only cancer and precancer age but also childhood and puberty, when most of the 50 per cent of patients with acanthosis nigricans not associated with cancer start to show signs of the cutaneous disorder. The different forms of behavior of the disease can be compared with each other.

The chief disadvantages of the human being with acanthosis nigricans as an object for genetic studies are that observation needed for valid conclusions in a single case will extend over long periods and that uncontrolled breeding and a host of nongenetic factors which have a bearing on cancer in human beings affect the studies. In the particular problem at hand, moreover, cancer occurs not in one but in many internal organs, although all cancers recorded are glandular. In addition, besides the probable linkage, there is evidence that another relationship exists between acanthosis nigricans and cancer, i. e., at times cancer activates acanthosis nigricans.

In this paper there is no speculation on the genetic mechanism which prevails in acanthosis nigricans and the accompanying cancer. It states the problem of the association of the cutaneous disorder with cancer and points out where research is needed before any conclusions can be drawn.

Monthly **74**:204 (May) 1947. Levine, B.: Acanthosis Nigricans, Arch. Dermat. & Syph. **55**:291 (Feb.) 1947. Robinson, S. S., and Tasker, S.: Acanthosis Nigricans Juvenilis Associated with Obesity: Report of a Case, with Observations on Endocrine Dysfunction in Benign Acanthosis Nigricans, ibid. **55**:749 (June) 1947. Babalian, L.: Juvenile Acanthosis Nigricans and Ichthyosis, ibid. **55**:411 (March) 1947. Werkö, L.: Acanthosis Nigricans Associated with Carcinoma of the Gallbladder and Plantar Hyperkeratosis: Report of a Case, Acta dermat.-venereol. **26**:70 (July) 1945. Laymon, C.: Acanthosis Nigricans (Juvenile Type), Arch Dermat. & Syph. **55**:144 (Jan.) 1947.

2. Strong, L. C.: The Non-Genetic Appearance of Various Types of Neoplasia in Experimental Animals, J. Cancer Research **12**:208, 1928.

Acanthosis nigricans is a benign cutaneous disease which involves the axillas (*A* of fig. 1), neck, external genitals, body folds, umbilicus, nipples, mucous membranes and the like. Clinically it is characterized by exaggeration of the furrows, papillary hypertrophy and brownish to blackish discoloration. Palmar and plantar hyperkeratoses, papillomas, pigmented spots and wartlike changes may accompany the main cutaneous changes.

In 50 per cent of the cases acanthosis nigricans develops almost simultaneously with internal cancer. However, acanthosis nigricans is not a cancer metastasis, nor does malignancy ever develop in the acanthotic lesion.

The cancer which accompanies acanthosis nigricans is of the glandular type. Alveolar arrangement of the primary growth or the metastatic tumors is described in many cases in which specimens were obtained at operation or autopsy. The primary cancer may occur in one of many organs. A study of the 208 cases of acanthosis nigricans associated with cancer reveals that the cancer originates in the thorax in 7 per cent and in the abdomen in 93 per cent. The former group comprises cases of mammary cancer, of cancer of the lung and of some questionable mediastinal tumors.[2a] Gastric cancer by far outnumbers other abdominal cancer which may occur in the liver, gallbladder, intestines, rectum, uterus and ovaries. Chorionic carcinoma has also been reported. These cancers associated with acanthosis nigricans possess no unique or remarkably new features. Although they occur in various organs, analysis and comparison reveal the homology of their qualities. They are highly malignant. They occur relatively frequently in young persons, and in old persons no mitigation is seen. They are characterized by early metastasis and inoperability. The mortality rate is high. No case of "cure" has been reported. The duration is short. The average period from discovery to death is twelve months.

In 1890 the first observers of the disease, Pollitzer[3] and, independently, Janovsky,[4] noted already that in their middle-aged patients cancer, or a suspected cancer, was associated with acanthosis nigricans. Later, however, it became apparent that cutaneous changes indistinguish-

2a. Lately, Kaufman and Tilley (Kaufman, W. H., and Tilley, R. F.: Acanthosis Nigricans: A Case Associated with Thyroid Malignancy, to be published) observed a highly anaplastic thyroid malignant growth in a 33 year old Negro woman.

3. Pollitzer, S.: Acanthosis nigricans, in Unna, P. G.; Morris, M.; Duhring, L. A., and Leloir, H.: Internationaler Atlas seltener Hautkrankheiten, Leipzig, L. Voss, 1890, vol. 10.

4. Janovsky, V.: Acanthosis nigricans, in Unna, P. G.; Morris, M.; Duhring, L. A., and Leloir, H.: Internationaler Atlas seltener Hautkrankheiten, Leipzig, L. Voss, 1890, vol. 10.

able from those described by Pollitzer, Janovsky and others occurred in young and healthy persons, in whom prolonged and extensive study did not reveal the presence of cancer. These observations led to the differentiation of two types of acanthosis nigricans, one called "malignant," because it was associated with cancer, and the other called "benign," because it lacked this association. Since the two types show the identical clinical picture and pathologic condition, all explanations of the disease should offer a solution for the two types. It was believed first that most of the cancers associated with acanthosis nigricans were located in the abdominal cavity and that, therefore, pressure from cancer or metastatic cancer on the sympathetic nervous system via the adrenals would cause the discoloring cutaneous changes. However, clinical investigation shows the fallacy of this theory. Seven per cent of cancers associated with acanthosis nigricans are located in the chest, and while the adrenals are often the site of metastatic cancer they are about as often free from all involvement. Illustrative is the recent report of an autopsy performed in Werkö's [1] case of acanthosis nigricans associated with carcinoma of the gallbladder. Abdominal metastasis was widespread. The noninvolvement of the adrenals was expressly noted. The proponents of the theory which stressed the role of the sympathetic nervous system must have been misled by the similarity of acanthosis nigricans and Addison's disease. In a few cases tests for adrenal insufficiency were undertaken. The Robinson, Power and Kepler test gave normal values in Kaufman and Smith's [1] case of acanthosis nigricans of the benign type. A test of urinary sodium chloride excretion showed no evidence of adrenal cortical insufficiency in Herold, Kaufman and Smith's [4a] case of acanthosis nigricans associated with gastric cancer in a 17 year old girl. Study of acanthosis nigricans shows, in contradistinction to Addison's disease, regional, not generalized, involvement of the skin and the discoloration as only part of the pathologic process of the skin. Nevertheless, the same theory of the disturbance of the sympathetic system was also advanced to account for the benign form. The concept was further extended to suggest a basis for various endocrine dysfunctions. However, in those cases of benign acanthosis nigricans in which laparotomy was performed, the sympathetic nervous system was uninvolved, and tabulation of diseases which occasionally are seen in a patient with acanthosis nigricans shows that no specific endocrine disorder occurs in any percentage significant enough to warrant basing any conclusion concerning the etiology of acanthosis nigricans on it.

4a. Herold, W. C.; Kaufman, W. H., and Smith, D. C.: Acanthosis Nigricans: Its Occurrence in Association with Gastric Carcinoma in a Seventeen Year Old Girl, Arch. Dermat. & Syph. **44**:789 (Nov.) 1941.

A comparison of the two types (table) will show where the similarities and differences of the two types lie. Both sexes are involved equally often (male 50 per cent and female 50 per cent). Each type comprises about the same number of cases (50.2 per cent without cancer; 49.8 per cent with cancer).[5] The cutaneous lesions in the two groups are essentially identical, but differences of possible significance of the two types have been noted. The distribution on the skin may show differences, since the lesions in some cases of benign acanthosis nigricans, especially those which start at birth, may be arranged unilaterally. The rest of the cases of benign disease show the same symmetric distribution which one sees in cases of malignant disease.

Similarities and Differences of the Two Types of Acanthosis Nigricans

Similarities		Differences	
Incidence	Each type comprises about 50 per cent	Distribution	Some cases of the benign type show unilateral involvement, the rest of the benign type and the malignant type show symmetric involvement
Sex	Male, 50 per cent Female, 50 per cent	Association with cancer	Present in malignant type; lacking in benign type
Clinical picture	Identical in the two types	Familial cases	Reported only in some cases of the benign type
Histology	Identical	Course	Spreading at onset; later stationary or regressing in benign type; spreading in malignant type
Distribution	Similar only when symmetrically distributed	Duration	Indefinite in benign type; death due to accompanying cancer in malignant type
		Age at onset	Cases of the benign type usually appear at birth, in early childhood or at puberty; cases of the malignant type occur mostly in middle-aged persons, but also in young and old persons

(There are 2 cases of malignant disease recorded [Becker[6] and Halty, Correa Delgado and Volpe[7]] in which unilateral involvement of acanthosis nigricans was maintained for a while before the disease progressed to symmetric almost generalized involvement of the skin at a time when a malignant neoplasm became widespread.) It is not surprising to see nevoid signs, such as familial occurrence, unilateral involvement and association with other nevi, in that type of disease which starts at birth

5. The addition of cases published after completion of this paper, changes the numbers to 50.3 per cent without cancer and 49.7 per cent with cancer.

6. Becker: Ein Fall von Acanthosis nigricans, Berl. klin. Wchnschr. **41**:69, 1904.

7. Halty, M.; Correa Delgado, B.; and Volpe, A. Acanthosis Nigricans, Rev. sud-am. de méd. et de chir. **4**:189 (March) 1933

or in early childhood. There are, indeed, many cases of benign acanthosis nigricans on record in which members of several generations of one family are involved. To the number of cases of unilateral acanthosis nigricans should be added some cases in which the diagnosis was unilateral acanthiform or ichthyosiform nevi and which in reality were cases of acanthosis nigricans. Babalian [1] presented a 33 year old man

Fig. 1.—*A*, acanthosis nigricans of the axilla of a patient at the age of 14 (1932). *B*, unilateral acanthosis nigricans of the right side of the abdomen and symmetric acanthosis nigricans of the axillas, neck, nipples, genitals and umbilicus. The patient was born with the unilateral nevus, and symmetric acanthosis nigricans developed at puberty (picture taken in 1932). *C*, unilateral acanthosis nigricans of the right side of the abdomen of the same patient in 1947, at the age of 29. *D*, right axilla of the same patient in 1947.

in whom the diagnosis was either acanthosis nigricans, juvenile type, or ichthyosis hystrix. This identity of unilateral nevus and acanthosis nigricans is well illustrated by the case of a boy whom I saw first in

1932, at the age of 14 (Curth [8]). He was born with a unilateral nevus on the abdomen, indistinguishable from acanthosis nigricans. At puberty, in addition, symmetric benign acanthosis nigricans developed (*B* of fig. 1). I saw him again in 1945 at the age of 27. The decided involvement of the right side of the abdomen had persisted (*C* of fig. 1), while, incidentally, the symmetric signs of acanthosis nigricans, which had been pronounced in 1932, had either completely disappeared or had become much paler (*D* of fig. 1). He showed many new pigmented nevi, especially on the upper part of the chest.

The study of the behavior of the cutaneous condition after onset is of great practical value. Benign acanthosis nigricans will spread at onset and will then become stationary or regress. Malignant acanthosis nigricans may after onset remain stationary for a while. It will then start to spread and involve new areas of the body. Invariably, at the same time, such extension is accompanied with the first manifestation of an internal cancer or by extension of a cancer already present. The difference of the rate and mode of propagation of the cutaneous changes of the two types seems to hinge on the different activating principle. In the benign type it acts only for a certain period, while in cases of malignant disease apparently the presence of cancer keeps acanthosis nigricans going. One arrives at this conclusion because the propagation of cancer and the propagation of acanthosis nigricans run parallel. This parallelism goes so far that even temporary or partial elimination of the cancer after operation or radiation has in some cases been accompanied with transitory improvement of acanthosis nigricans. In the end, however, death from cancer ensues, while the (still benign) cutaneous disease has continued to involve larger areas.

Completely different from each other are the curves for the age at onset of the two types (figs. 2 and 3 [9]). The curve for the age of onset of the malignant type (fig. 2) follows more or less the curve for the age of onset in a group with glandular cancer (without acanthosis nigricans). It is, therefore, not surprising that some children and many young persons (33 cases in persons under 31) are among the victims of the malignant type of the disease. Most patients, however, are middle aged or old. The peak of the curve for the onset of the benign type (fig. 3) occurs at the age of puberty and seems to taper off with the end of adolescence. It is here that research is needed. Which principle of puberty and adolescence is responsible for the activation of acanthosis

8. Curth, H. O.: Benign Type of Acanthosis Nigricans: Etiology, Arch. Dermat. & Syph. **34**:353 (Sept.) 1936.

9. To the number of cases of acanthosis nigricans of the benign type starting at puberty, 2 should be added which were recently reported by Robinson and Tasker [1] and by Laymon.[1]

nigricans? In this connection an observation by Jadassohn [10] deserves mention. The author described a family in which several members (mother, daughter and son) showed benign acanthosis nigricans. In the mother and daughter acanthosis nigricans appeared with the first period of menstruation. One daughter, 10 years old, who had not yet menstruated, was free from acanthosis nigricans.

Is it the sterols which exert the activating influence on acanthosis nigricans and are they normally or pathologically increased in an adolescent with acanthosis nigricans? Can their action in patients in whom acanthosis nigricans is to develop be compared to results obtained with estrogenic hormone on the potential capacity of pigment formation in cutaneous areas where such an inherent capacity had been present? (Davis, Boynton, Ferguson and Rothman.[10b]) Can the inciting influence of the steroid hormones be compared to the influence which cancer or some substance related to it exerts on acanthosis nigricans

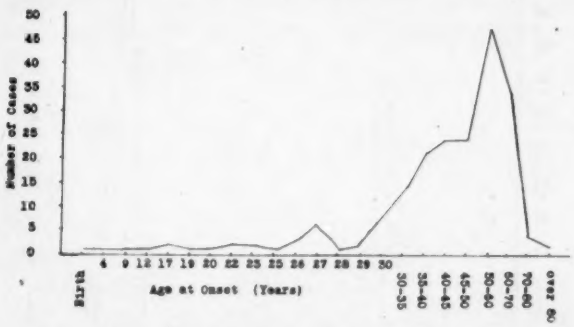

Fig. 2.—Incidence of the malignant type of acanthosis nigricans.

in the malignant type? Study of the two curves would suggest that possibility, but research is needed to prove it. It would be fortunate if some dogs with acanthosis nigricans and internal cancer were again found for experimental purposes. Two such cases have been reported (Schindelka [11] and Curth and Slanetz [12]).

It is evident by now that the presence of acanthosis nigricans and cancer in the same patient is not coincidental. Fifty per cent of per-

10. (*a*) Jadassohn, W.: Acanthosis nigricans, kombiniert mit Stoffwechselstörung (pathologische Fettsucht), Zentralbl. f. Haut- u. Geschlechtskr. **21**:43, 1927. (*b*) Davis, M. E.; Boynton, M. W.; Ferguson, J. H., and Rothman, S.: Studies on Pigmentation of Endocrine Origin, J. Endocrinol. **5**:138 (March) 1945. The Role of Estrogens in Physiologic Hyperpigmentation, editorial, J. A. M. A. **128**:734 (July 7) 1945.

11. Schindelka, H.: Hautkrankheiten bei Haustieren, Leipzig, W. Braumüller, 1898, p. 415

12. Curth, H. O., and Slanetz, C. A.: Acanthosis Nigricans and Cancer of the Liver in a Dog, Am. J. Cancer **37**:216, 1939.

sons with a noncancerous disease also have cancer. In these cases the relationship between acanthosis nigricans and cancer is definite and close. If only persons in the cancer age would show the association of acanthosis nigricans and cancer, one could perhaps argue that cancer might be present regardless of acanthosis nigricans. However, the fact that many young persons suffer from acanthosis nigricans and cancer shows that the combination of these two factors is governed by definite rules.

One has repeatedly asked what occurs first in a patient who exhibits the malignant type of the disease: cancer or acanthosis nigricans?

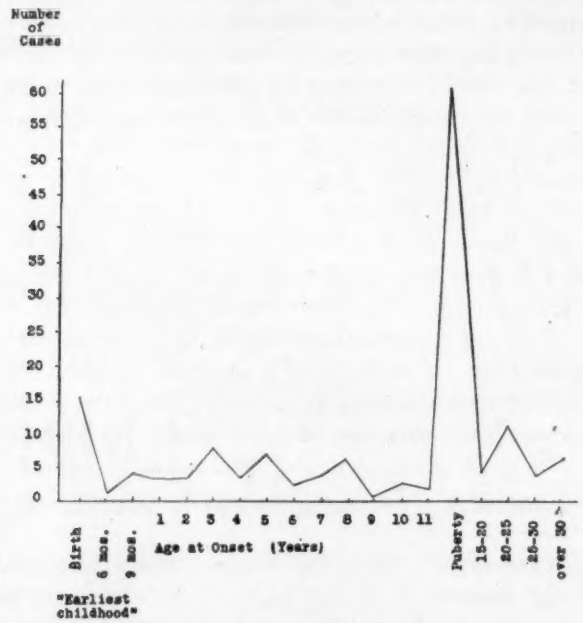

Fig. 3.—Incidence of the benign type of acanthosis nigricans. Some of the patients in the "over 30" group belong to a family in which in three generations the onset was after the thirty-fifth year.

Figure 4 answers this question. (The material in figure 4 is based on the data from 142 cases, the only ones which furnish details of the time of onset.) This shows that the two factors are chronologically independent of each other and that neither is the primary one to which the other is a consequence. While in many, 87 cases (88, including Werkö's [1] case), the cutaneous disease and the internal tumor appear at about the same time (with the chance that the more easily perceptible cutaneous change is discovered first), acanthosis nigricans may appear after the manifestation of cancer or before it. In 30 cases the cancer had been present for some time, treated or untreated, before acanthosis

nigricans appeared. Theoretically, of course, there is not too much time left for the subsequent appearance of acanthosis nigricans, because the duration of life in these patients is short. Often (in 25 cases) acanthosis nigricans appears before the cancer, in some cases exceedingly long before the cancer becomes manifest. The longest interval on record between the appearance of acanthosis nigricans in the first place and the subsequent manifestation of cancer is in the case of a girl in whom eighteen years after the appearance of acanthosis nigricans, at the age of 27, multiple cancers of the breast developed (Freund[13]). In other cases cancer followed acanthosis nigricans after periods of fifteen (2 cases) and eleven years (2 cases).

It is because of these long periods when acanthosis nigricans exists without apparent cancer and also because of the fact that the cancers

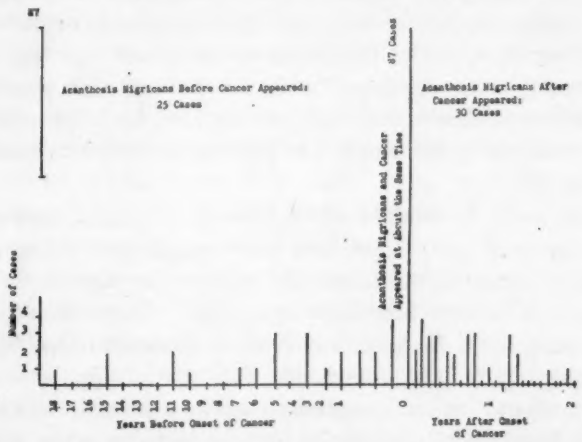
Acanthosis Nigricans Before Cancer Appeared: 25 Cases
Acanthosis Nigricans and Cancer Appeared at About the Same Time
87 Cases
Acanthosis Nigricans After Cancer Appeared: 30 Cases
Number of Cases
Years Before Onset of Cancer
Years After Onset of Cancer

Fig. 4.—Onset of the malignant type of acanthosis nigricans in relation to the appearance of cancer in the same patient.

accompanied with acanthosis nigricans comprise only an infinitesimal number among all cancers that the activating influence of cancer on acanthosis nigricans does not wholly solve the problem of their occurrence in combination.

What kind of relationship is it, then, that exists between acanthosis nigricans and cancer, and would the explanation also account for that type of the cutaneous disease in which cancer is absent in the clinical picture?

Clinical data on the patients' cancer and personal and family history have in general been vague and incomplete, but one fact has recurred with sufficient frequency to draw the attention of some observers of

13. Freund, E.: Cas d'acanthosis nigricans: Apparition d'un carcinome après seize années, Rev. franç. de dermat. et de vénéréol. 7:450, 1931.

the disease (Moncorps [14] and Stihl [15]). That is the frequent occurrence of cancer among the relatives of patients with acanthosis nigricans. I have gathered 24 cases of patients with (benign and malignant) acanthosis nigricans in whose relatives glandular cancer was present. In 3 cases, several members of the family were involved. Among the families in which one member had acanthosis nigricans and another one cancer was that of the aforementioned boy (Curth [8]), suffering from neviform and symmetric benign acanthosis nigricans. His mother died of colloid carcinoma of the rectum at the age of 36. As of the time of writing he has one son, aged 19 months, who is free from acanthosis nigricans. He has a large palm-sized pigmented nevus on the right thigh. Similarly located nevi have frequently occurred in the mother's family. These data from family histories as they are given at present do not signify much. The descendants of patients with benign and malignant acanthosis nigricans should be included in the study. All members of the family should be listed and the incidence of cancer among them compared with the incidence of cancer in the general population. Only then will one be able to judge whether the percentage of cancer in the families of patients with acanthosis nigricans is significantly high.

If the fact could be established that cancer, the same type of cancer which is associated with acanthosis nigricans in the malignant form of the disease, occurs in an unusually high percentage in the families of patients with benign acanthosis nigricans, cancer would keep its significance also for a form in which it is absent during the lifetime of the patient. If it is assumed that the relationship between acanthosis nigricans and cancer is genetic it may be possible to explain the strange fact that two related factors in one instance occur together in one person (malignant type) while in the other instance they occur dissociated in separate but genetically related persons. In an analysis of the time relationship between acanthosis nigricans and cancer it was observed that the two factors are chronologically independent of each other and that neither is the primary one to which the other is a consequence. In a genetic relationship between the two, one would not expect either disease to be the more important causative factor. Not much is yet known about the inheritance of glandular cancer in general and the glandular cancer associated with acanthosis nigricans in particular. This much, however, can be said: The hereditary factor is of more importance in glandular than in squamous cell cancer (Schinz

14. Moncorps, C.: Acanthosis nigricans, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, pp. 372-402.

15. Stihl, J.: Zur Kenntnis der Acanthosis nigricans, Inaug. Dissert., Leipzig, 1920.

and Buschke[16]). It is the glandular form which is associated with acanthosis nigricans. Morton,[16a] after mentioning the occurrence of gastric cancer in 1 set of homologous twins and of cancer of the breast in another set added that although it is difficult to establish by exact scientific methods, there is a certain amount of evidence that cancer does tend to run in families.

In conclusion, it should be said that before the etiologic significance of acanthosis nigricans, which to me seems centered in the relationship of acanthosis nigricans and cancer, can be solved, more research is needed.

As outlined before, a study of the substances which seem to activate acanthosis nigricans is important. The sterols in the benign type and the cancer or other carcinogenic substances in the malignant type would be the first logical objects for study.

In the matter of the genetic relationship between acanthosis nigricans and cancer more study is needed to establish the malignant type of acanthosis nigricans as a genodermatosis. Such signs have been observed for the benign type in the cutaneous lesion itself (familial occurrence, unilateral distribution and onset at birth) and in accompanying nevi. There have been other cases reported which either were associated with epidermal nevi (Franks,[17] type of acanthosis nigricans undetermined) or in which acanthosis nigricans started as a unilateral lesion and later became malignant and part of symmetric involvement (Becker,[6] Halty, Correa Delgado and Volpé[7]). Besides a more scientific approach to the family history of patients with acanthosis nigricans with regard to cancer, a more comprehensive tabulation of family members who suffer from benign acanthosis nigricans is needed to determine the type of inheritance which prevails in cancer and acanthosis nigricans.

Not directly pertaining to the relationship between the two factors, but of practical and theoretic value, would be a study for the detection of abortive forms of the cutaneous disease. If these cases can be regarded as of acanthosis nigricans they would greatly enhance the material for study, which definitely suffers from the low incidence of acanthosis nigricans. There are typical, but mild, changes of acanthosis nigricans sometimes seen in the axillas of nonobese patients. The presence and duration of the cutaneous changes are in most cases unknown to the patient. To such a case of abortive acanthosis nigricans which was

16. Schinz, H. R., and Buschke, F.: Krebs und Vererbung, Leipzig, Georg Thieme, 1934

16a. Morton, J. J.: The Cancer Problem, J. A. M. A. **135**:957 (Dec. 13) 1947.

17. Franks, A. G.: Acanthosis Nigricans, Arch. Dermat. & Syph. **47**:97 (Jan.) 1943.

mentioned in my last paper on the subject can be added another: A dark-haired woman, aged 24, had typical axillary changes, which have remained stationary during observation of three years. There were no other signs of acanthosis nigricans on the body. The patient could give no information regarding the duration of the cutaneous disease, since she had not been aware of it. It had never caused any symptoms. Her family history showed that her mother had died of pneumonia and that her father had died of cancer of the rectum. There seems to be a number of obese persons who exhibit the typical cutaneous changes of acanthosis nigricans to a mild degree in the axillas, some also on the neck and other favorite areas. Such cases have recently been described by Robinson and Tasker [1] and Rothman and Shapiro.[1] While the histologic characteristic changes in cases of fully developed disease are easily recognized, the clinical picture and the histologic variation of mild changes are not particularly characteristic. The disappearance of mild cutaneous changes in obese patients when exposure to sun is reduced or obesity and its accompanying mechanical factors of maceration, perspiration and friction are lessened casts some doubt on the diagnosis of some instances reported as acanthosis nigricans. On the other hand, an additional number of cases of the malignant type in cancer hospitals may be discovered if special attention is directed to routine inspection of the axillas of patients with far advanced disease for cutaneous changes of acanthosis nigricans.

SUMMARY

Acanthosis nigricans, a benign cutaneous disease, occurs in two types. The similarities and differences of the two types are listed, and conclusions as to the different mechanisms governing their behavior are drawn. The type of cancer which occurs in connection with acanthosis nigricans is studied. The etiologic aspect of acanthosis nigricans seems centered in the relationship of acanthosis nigricans and cancer. Evidence points to a genetic relationship between the two. More research is needed especially with regard to the activating influence on acanthosis nigricans of the sterols and of some properties of the cancer. While the benign type of the cutaneous disease has been established as genodermatosis, the malignant type should also be regarded from that angle. A more scientific approach to the family history of patients suffering from acanthosis nigricans, with regard to cancer, and of patients with familial benign acanthosis nigricans is needed. More attention should be paid to the study of abortive acanthosis nigricans.

35 East Eighty-Fourth Street.

ROLE OF THE LIVER IN CONGESTIVE ECZEMA

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THERE have been numerous attempts to show a relationship between certain of the cutaneous diseases and disturbances in hepatic function. This is not surprising when one considers that the skin is a parenchymatous organ many of the functions of which are similar to those of the liver. Such, for example, are the storage of carbohydrate, participation in cholesterol and sulfur metabolism, the synthesis of certain pigments and vitamins and the sharing of reticuloendothelial functions.

Bulkley,[1] some thirty years ago, was one of the first to point out a relationship of hepatic function to cutaneous disorders, but his work was done before the days of the present laboratory tests of hepatic function and is of only historic interest. Falchi[2] in 1927 reported that a functional disturbance of the liver was observed in 40 per cent of the 96 patients with eczema that he studied. In 1930 Matsunobu[3] reported that a functional disturbance of the liver existed in 30 per cent of his patients with various cutaneous diseases. In patients with eczema (unqualified) he found 23 per cent had disturbance of the liver. Later Rocchini[4] noted malfunctioning of the liver by the rose bengal test in his patients with eczema. In 1936 Kitamura and his associates[5]

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, June 12, 1946.

1. Bulkley, L. D.: Diseases of the Skin in Relation to Hepatic and Renal Disorders, J. Cutan. Dis. **30**:670-680, 1912.

2. Falchi, G.: Richerche sulla funzionalita etatica nell'eczema, Gior. ital. di dermat. e sif. **68**: 704, 1927.

3. Matsunobu, T.: Eczematous Transformation of Skin and Liver Function, Jap. J. Dermat. & Urol. **30**:86 (Aug.) 1930.

4. Rocchini, G.: La prova del rosa bengala in alcune dermatosi con speciale riferimento all'eczema, Gior. ital. di dermat. e sif. **76**:1075-1089 (Aug.) 1935.

5. Kitamura, S.; Murayama, M.; Yajima; Mori, and Uchimura: Ueber die nutritiven allergischen Hautkrankheiten unter Berücksichtigung der Umstände der Verdauungsorgane, Jap. J. Dermat. & Urol. **40**:167-168 (Nov. 20) 1936.

reported that 11 out of 14 of their patients with allergic diseases of the skin had disturbances of hepatic function as measured by the galactose tolerance test.

Burgess and Rabinowitch [6] maintained that increase of bilirubin in the blood and increases of urobilinogen in the urine are the earliest signs of hepatic disturbance. They performed such determinations in 216 patients who had twenty-seven different cutaneous diseases, and they noted that these values were abnormal in about half of their patients. They concluded that disturbance of the liver is common in dermatoses but pointed out that the disturbance may be either the cause or the effect of the disease of the skin. Hubner [7] examined 14 older patients with pruritus and found hyperbilirubinemia in 5 patients and impaired hepatic function, as determined by the galactose tolerance test, in 2 patients.

Hence there is much evidence to point to the existence of malfunctioning of the liver in certain diseases of the skin. However, one must bear in mind that disturbance of the liver may be the cause of the cutaneous diseases or vice versa, or that both may be due to some extraneous common cause.

Many tests of hepatic function have been described, but only a few have withstood the test of time and have remained of practical importance. There is no one test that reflects the state of function of the liver as a whole. The most accurate evaluation is made by consideration of several tests at the same time.[8]

In the patient with severe damage to the liver, particularly when it is associated with jaundice, there is usually no difficulty in demonstrating the damage by laboratory tests or in following the progress of that disease in either direction. However, this study is concerned with mild damage to the liver without jaundice, and the determination of this degree of damage is difficult. Here the excretion of sulfobromophthalein sodium, the prothrombin response to vitamin K, the determination of serum proteins and the albumin-globulin ratio offer the most reliable information.[9] For the purposes of this study we were limited to the sulfobromophthalein sodium test and determination of the blood protein, including the albumin-globulin ratio.

The sulfobromophthalein sodium test was performed by the intravenous injection of the dye in doses of 5 mg. per kilogram of body

6. Burgess, J. F., and Rabinowitch, I. M.: Bile Pigment Metabolism in Diseases of the Skin, Arch. Dermat. & Syph. **35**:932-941 (May) 1937.

7. Hubner, K.: Hyperbilirubinämie und Pruritus, Arch. f. Dermat. u. Syph. **175**:508-514, 1937.

8. Allen, J. G.: Clinical Value of Functional Tests of Liver: Review with Special Study of Plasma Prothrombin, Gastroenterology **3**:490-505 (Dec.) 1944.

9. Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulfalein Test for Hepatic Function, J. A. M. A. **84**:1112-1114 (April 11) 1925.

weight and then by determining the percentage of the dye retained in the circulating blood at thirty and forty-five minute intervals. The normal limit for retention of the dye was considered to be 5 to 7 per cent in thirty minutes with no retention in forty-five minutes.[10] The normal value for total serum proteins is 6.5 to 8.0 Gm. per hundred cubic centimeters of serum with a normal albumin-globulin ratio of 3:1 to 1.7:1. When the total protein is less than 5.5 Gm., or when there is inversion of the albumin-globulin ratio, and no other cause can be determined (e. g. renal failure, starvation), damage to the liver is evidenced.

CONGESTIVE ECZEMA

The commonest form of congestive eczema is varicose eczema. Patchy eczema, usually of the legs, sometimes of the arms and trunk and associated with varying degrees of edema of the skin, we believe, should also be classified in this group. Hazen[11] called attention to the common occurrence of hypertension and of early cardiac failure in many cases of this kind.

Our interest in the damaged liver as a source of edema was first aroused by the occurrence of a generalized patchy eczema in a patient with severe jaundice with edema (case 1) and of congestive eczema of the legs in a man who had no cardiovascular or renal disease to account for his edema but did have an enlarged liver (case 2). We then performed tests of hepatic function in a number of patients with various cutaneous diseases. In several patients with congestive eczema we found evidence of damage to the liver. Therapy directed at improving the function of the liver helped materially in improving both the disease of the skin and the patient's general health.

CASE 1.—J. K., a white man aged 52, was admitted to the hospital with severe jaundice, generalized anasarca and ascites. While he was in the hsopital large patches of eczema developed on all parts of his body. No tests of hepatic function were done on this patient—they seemed hardly necessary. However, he ultimately recovered, and his eczema disappeared with the subsidence of his edema.

CASE 2.—E. P. W., a white man aged 61, an alcoholic addict, presented edema of the legs from below the knee to the feet with congestive eczema in the edematous areas. He was carefully examined for cardiovascular and for renal disease by his internist. Neither disease was present. Subsequently, we found the liver 4 fingerbreadths below the costal margin. His sulfobromophthalein sodium test showed 30 per cent retention in thirty minutes and 10 per cent in forty-five minutes. The albumin-globulin ratio was 1.6:1.

CASE 3.—E. M. V., a white man aged 62, had stubborn and recurring eczema of the legs with patches of eczema on the arms and a few small patches on

10. White, F. W.: Liver Function Tests, Bull. New England M. Center 8:14-20, 1946.

11. Hazen, H. H.: Skin Diseases Precursors to Serious Disease, with Special Reference to Hemostatic Eczema, Am. Med. **38**: 355-358 (Sept.) 1932.

the trunk. He was not alcoholic but gave a history of syphilis many years before, though at the time of our examination he was seronegative. This man was treated for several months each year for three years with only partial improvement, until the test of hepatic function showed definite damage to the liver. Retention of dye was 30 per cent after thirty minutes and 5 per cent after forty-five minutes. His albumin-globulin ratio was 1.8:1. His total protein was 5.8 Gm. per hundred cubic centimeters.

Case 4.—E. T., a white man aged 59, was a large overweight person who presented severe eczema of the legs and hands associated with pitting edema of the legs. This man had clinical evidence of congestive heart failure and an enlarged liver. His test of hepatic function showed decided damage to the liver. It is recognized that in the presence of cardiac edema the test is not entirely reliable. Retention of dye was 55 per cent after thirty minutes and 40 per cent after forty-five minutes, and his albumin-globulin ratio was 1.2:1.

Case 5.—Mrs. M. C., white, aged 47, was obese. She presented severe eczema of the extremities, which was especially severe on the hands. The results of the cardiovascular examination were normal for her age and weight. She had

Table 1.—*Summary of Cases Reported*

Case	Sulfobromophthalein Sodium Retained (Percentage)		Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Albumin-Globulin Ratio
	In 30 Min.	In 45 Min.			
2	30	10	3.8	2.4	1.6:1
3	30	5	3.6	2.0	1.8:1
4	55	40	3.7	3.0	1.2:1
5	10	2	4.6	2.9	1.6:1
6	12	8	3.28	2.18	1.5:1
7	12	4	4.0	1.8	2.2:1
8	15	5	3.4	2.5	1.3:1

evidence of damage to the liver which was not severe. Retention of dye was 15 per cent after thirty minutes and 2 per cent after forty-five minutes, and the albumin-globulin ratio was 1.6:1.

Case 6.—Mr. G. A. B., white, aged 60 and somewhat underweight, presented chronic patchy eczema of the ankles, which had recurred off and on for some years and had had all the usual treatment including roentgen ray. His liver was not enlarged, but his test of hepatic function showed mild damage to the liver. Retention of dye was 12 per cent after thirty minutes and 8 per cent after forty-five minutes and the albumin-globulin ratio was 1.5:1.

Case 7.—Mr. L. W., aged 72, had patchy eczema of the legs and of the anal region. His liver was not enlarged, but his sulfobromophthalein sodium test showed 12 per cent retention in thirty minutes and 4 per cent in forty-five minutes, and his albumin-globulin ratio was 2.2:1. His total protein was 5.8 Gm. per hundred cubic centimeters.

Case 8.—Mr. J. M., aged 64, white, had congestive eczema of the legs associated with varicose veins. His sulfobromophthalein sodium test showed 15 per cent retention in thirty minutes and 5 per cent in forty-five minutes. His albumin-globulin ratio was 1.3:1, and his total protein was 5.9 Gm. per hundred cubic centimeters.

CONTROLS

Results of tests in 8 patients with other than congestive eczema are presented in table 2. All these results were normal except for the last patient, who had psoriasis. This patient had beginning congestive heart failure, which may account for his abnormal hepatic function.

TREATMENT

The patients in this group were given the following treatment for disease of the liver: (1) high protein, high carbohydrate diet and low fat diet, (2) injections of crude liver extract, (3) large doses of vitamin B complex and (4) supplemental feeding of protein hydrolyzates.

Several of the patients were entirely relieved of their eczema, and all of them were improved by this management. It was noted also that the general health of all these patients was benefited.

TABLE 2.—*Results of Tests in Eight Patients with Other than Congestive Eczema*

Case	Diagnosis	Sulfobromophthalein Sodium Retained (%) In 30 Min.	In 45 Min.	Albumin, Gm.	Globulin, Gm.	Albumin-Globulin Ratio
1a	Patchy eczema of neck and shoulders	5	0	3.35	2.65	1.3:1
2a	Subacute generalized lupus erythematosus	0	0	2.73	3.3	0.8:1
3a	Congestive eczema (varicose)	0	0	4.85	1.9	2.5:1
4a	Generalized eczema	4	0	3.45	2.67	1.3:1
5a	Congestive eczema	7	0	6.1	3.3	1.8:1
6a	Generalized atopic dermatitis	0	0	5.25	3.85	1.4:1
7a	Congestive eczema of legs	0	0	4.2	1.8	2.4:1
8a	Seborrheic dermatitis	5	0	5.4	3.2	1.7:1

EXPERIMENTS WITH ANIMALS

The only references which we can find in the literature to experiments with animals are two Japanese articles. One of these was not available for review. Matsunobu[8] produced eczema in rabbits and found damage to the liver by tests of hepatic function in these animals.

We attempted the reverse of this procedure. Six rabbits received injections of 2 cc. of carbon tetrachloride per kilogram given twice at three day intervals according to the method recommended by King, Harrison and Delory.[12] Three of the 6 rabbits died of acute toxic hepatitis as shown by postmortem examination. On the remaining 3 rabbits and on the 6 control rabbits, croton oil full strength and in serial dilutions up to 1:16 were applied to the shaved back of the animals. However, no appreciable differences in the irritation produced were noted between the rabbits with damaged livers and those used as controls.

12. King, E. J.; Harrison, C. V., and Delory, G. E.: Galactose Tolerance Test in Experimental Liver Necrosis, Lancet **2**:541-543 (Nov. 2) 1940.

SUMMARY AND CONCLUSIONS

Previous reports of the relationship of disturbed hepatic function to cutaneous disease have been briefly reviewed. A small series of cases of congestive eczema in which disturbed hepatic function was demonstrated are reported. Clinical improvement was secured in patients by instituting measures aimed at improving hepatic function. With the tests used in the small number of control cases of various dermatoses examined impaired hepatic function was not demonstrated. This is contrary to observations of other authors, most of whose reports, however, are based on larger series of cases.

It is suggested that patients who have congestive eczema (and possibly other cutaneous diseases) that proves recalcitrant to treatment might well be studied for malfunction of the liver. If the malfunction is noted therapy directed toward improving hepatic function should be instituted.

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ABSTRACT OF DISCUSSION

Dr. Lloyd W. Ketron, Baltimore: It is gratifying to hear a paper presenting evidence of an etiologic relationship between some of the eczematous dermatoses and disorders of the internal organs. I must confess that after seeing many patients with eruptions of this nature who have had thorough medical studies in various institutions, I have become skeptical as to the fruitfulness of internal surveys or of special studies of certain organs in the approach to most dermatologic problems. There must be, however, such a relationship in some cases, and Dr. Eichenlaub is to be congratulated on pointing out one field of investigation that may be fruitful.

Dr. E. William Abramowitz, New York: I am sure that every one welcomes an experimental approach to the problem of certain types of eczematous eruptions which fail to respond to present methods of treatment. A rational therapeutic measure in such cases should follow, provided that the clinical and laboratory determinations in many cases of similar nature are present.

Frank Smithies, among others, reported on "Defective Liver Function as a Cause of Chronic Endogenous Skin Lesions" (*Ann. Int. Med.* **3**:1201, 1930). Chemical, roentgenologic, duodenal siphonage and serologic studies, in a total of 9 cases (psoriasis, urticaria, eczema) indicated chronic inflammation of the liver and/or of the biliary passages in these patients. The dermatoses disappeared or improved when hepatic function was restored by suitable systemic measures with little or no local medication.

I was interested in this subject at one time, as several patients with generalized neurodermatitis had shown considerable improvement after duodenal lavage for a concomitant biliary disturbance. I followed this lead in several other similar dermatoses but soon became discouraged because of the absence of clinical and laboratory signs of hepatic or biliary disease.

Disturbances of the liver and of the biliary apparatus are not always accompanied by visible cutaneous lesions. On the other hand, certain forms of hepatitis, especially forms due to drugs, are associated with cutaneous lesions. The latter disappear when treatment is directed at restoring the liver to its normal activity. Investigations of this sort are valuable, especially in those resistant eczematous dermatoses that remain the *bête noire* of dermatologists.

DR. FRED D. WEIDMAN, Philadelphia: It is not difficult to think of examples of the association of hepatic and cutaneous diseases. Many physicians recall the studies of erythema multiforme by Osler, in some of which cases recurrent erythema multiforme terminated after excision of the gallbladder. We know, too, of the pulsating angiomas with which there is associated cirrhosis of the liver, but Dr. Eichenlaub's subject is a narrower one than that; it has to do only with the matter of a possible relationship between congestive eczema and hepatic disease.

After all, when one thinks of the multiplicity of function of the liver, it would be surprising if there would not be occasional circumstances under which the circulating products of hepatic function produced deleterious effects on the skin. Naturally, there would be individual variation similar to that in syphilis outlined by Dr. Wile. The desideratum is to put one's finger precisely on this or that particular upset in hepatic function and on this or that particular peculiarity in the "constitutionalism" of the individual. Probably it is the old story that "time will tell"; that is, when our technics for discovering this and that special function of the liver have progressed further, it will be possible to discover combinations of circumstances joining vascular damage in the skin with abnormalities of hepatic function. In any event, it is proper that when the occasion presents, as here with Dr. Eichenlaub, the attempt should be made to chart our position with the technics now available.

Incidentally, in experimentations on the skin of animals the pig is the animal of choice if one can engineer its housing and handling. The skin of pigs has the closest anatomic and physiologic approach to the skin of man; this is true also of the kidney.

RELATION OF KERATOSIS SEBORRHEICA AND KERATOSIS SENILIS TO VITAMIN A DEFICIENCY

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IT HAS been shown that deficiency in vitamin A results in follicular hyperkeratosis.[1] Other lesions, including xeroderma, alopecia, ichthyosis and lichen planus, have been attributed to the same deficiency.[2] No reference was found to the possible part played by vitamin A deficiency in the development of keratosis seborrheica or keratosis senilis.

In this study, 100,000 units of vitamin A were given daily for from fifteen to twenty-three months, with an average of nineteen and eight-tenths months, to a group of 50 patients. Three members of an original group of 53 were lost, 2 by parole and 1 by death. Except for 2 who were hospital employees, these were patients of Western State Hospital. This made possible an unusual degree of control of persons observed. Age grouping was as follows: ages 40 to 50, 8 persons; 51 to 60, 18 persons; 61 to 70, 11 persons; 71 to 80, 8 persons and 81 to 90, 5 persons. These figures are not considered statistically significant, but are given for the sake of specificity concerning the important etiologic factor of age. Of the group, 7 were men, the remainder being women. Twenty-eight had both seborrheic and senile keratosis; 20 had only seborrheic and 8 had only senile keratosis.

A control group consisted of 30 hospital patients with the same lesions and age grouping as those in the treatment group. No member was lost from the control group.

All subjects appeared in reasonably good general health; no decidedly emaciated or debilitated patient was followed. No major medicational

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Read at a meeting of the Indiana State Association of Pathologists on Jan. 19, 1947.

From the Department of Pathology, Indianapolis City Hospital, and the Departments of Pathology and Internal Medicine, Western State Hospital, Fort Steilacoom, Wash.

1. Frazier, C. H., and Hu, C. K.: Cutaneous Lesions Associated with Deficiency in Vitamin A in Man, Arch. Int. Med. **48**:507-514 (Sept.) 1931.

2. Frazier and Hu.[1] Carleton, A., and Steven, D.: Keratosis Follicularis: Study of Four Cases, Arch. Dermat. & Syph. **48**:143-150 (Aug.) 1943.

regimen, such as arsenical, was employed (except for the vitamin). Diet was unchanged throughout the period of observation. It was not recorded in detail, but it did not appear grossly deficient and was considered ample in comparison with diets available elsewhere under similar conditions.

Specimens of skin were removed from all subjects, for biopsy, at the beginning and close of the study, and in a few cases at intervals during the study. The "beginning" specimens consisted in virtually every case of representative lesions of the aforementioned types, together with adjacent skin. The "closing" specimens were from partly cleared lesions, sites previously occupied by lesions, or persisting portions (3 cases) of large lesions, the same lesions having been sampled at the beginning.

Tissue was fixed by immersion in 4 per cent solution of formaldehyde U. S. P. and was embedded in paraffin and prepared with hematoxylin and eosin, combined Bodian and Masson method [3] and Weigert's fuchselin method for elastic fibers, counterstained with ponceau-fuchsin, orange G and light green. In a few cases Ranson's pyridine silver method for nerve fibers, sudan IV for fat and ultraviolet fluorescence for vitamin A were employed.

As mentioned previously, all patients under treatment had seborrheic keratosis or senile keratosis or both. These lesions were defined according to common usage and discussions available in standard textbooks.[4] Keratosis seborrheica was seen chiefly about the trunk, occasionally occurring on the face. It was seen as a well circumscribed raised plateau-like nodule of soft rubbery consistency, varying from gray and tan to dark brown or almost black. Keratosis senilis appeared on the face, neck and upper extremities. It was seen as a relatively poorly outlined flat gray area of firm scaly roughening. Microscopically, keratosis seborrheica was characterized by decided acanthosis and the formation of intraepithelial keratin plugs. Keratosis senilis showed less widening of the rete layer, but more irregularity of basal outline and more downward penetration of epithelial pegs, frequently with beginning disorder of cell structure; the surface presented relatively decided hyperkeratosis, often of a warty type.

RESULTS

No change of note was observed in the control group.

In the study group the effect of treatment was manifest, although relatively slow in appearing. Keratosis seborrheica and keratosis senilis responded similarly to administration of the vitamin. Usually after

3. Dublin, W. B.: Combined Bodian and Masson Staining Method Applied to Skin, Arch. Dermat. & Syph. **50**:361-362 (Dec.) 1944.

4. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

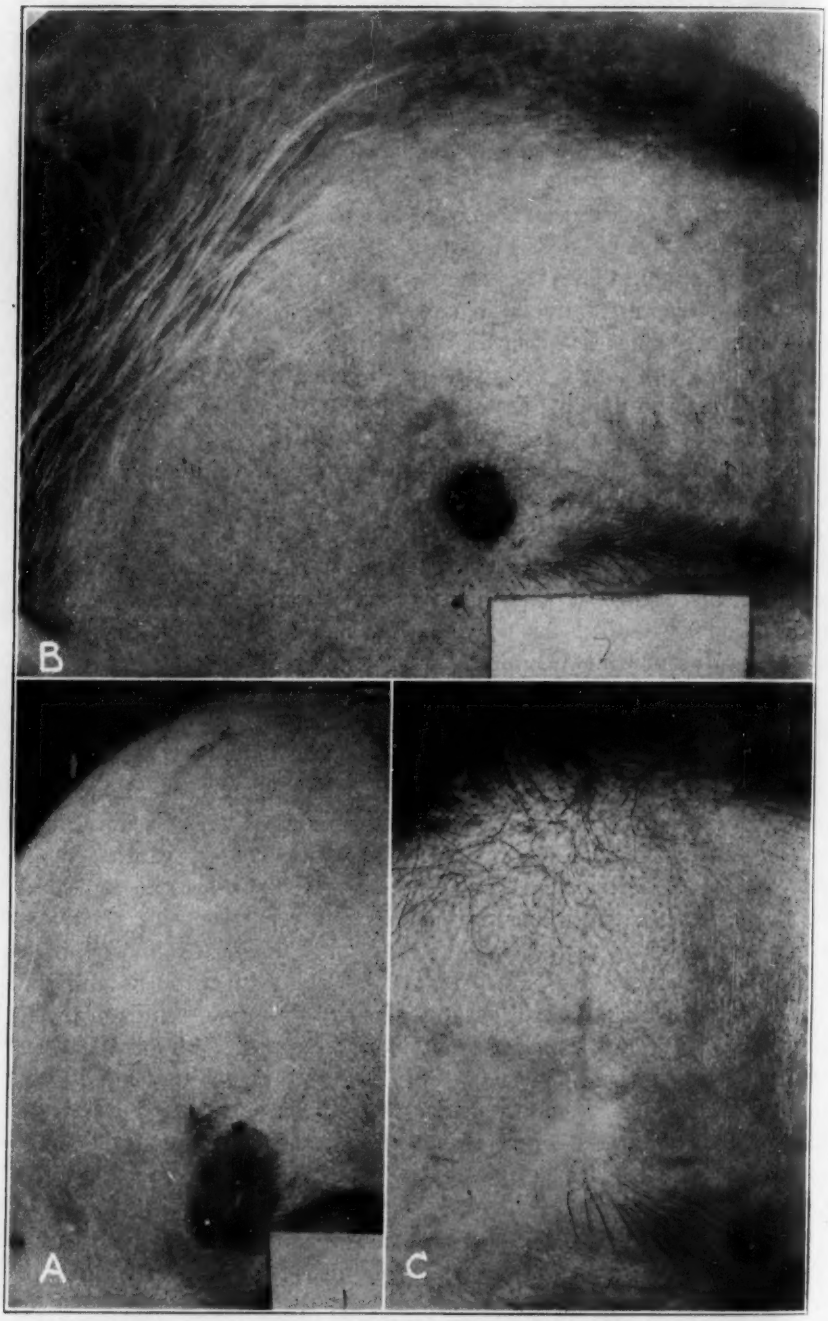

Fig. 1.—*A*, a large pigmented lesion of keratosis seborrheica of the forehead of a patient; the hair is sparse, fine and white. *B*, the same patient after five months' treatment with 100,000 units of vitamin A daily. The lesion is about three-quarters gone, and the hair is much thicker and darker. *C*, the same patient after eighteen months' treatment. The lesion has disappeared completely, leaving a small area of slight scarring. A thick crop of black hair has grown.

three or four months' treatment lesions began to regress, with flaking off of keratin. The lesions became gradually smaller and softer and became more translucent. In 13 cases all grossly identifiable lesions disappeared completely. In 5 instances no improvement resulted. In

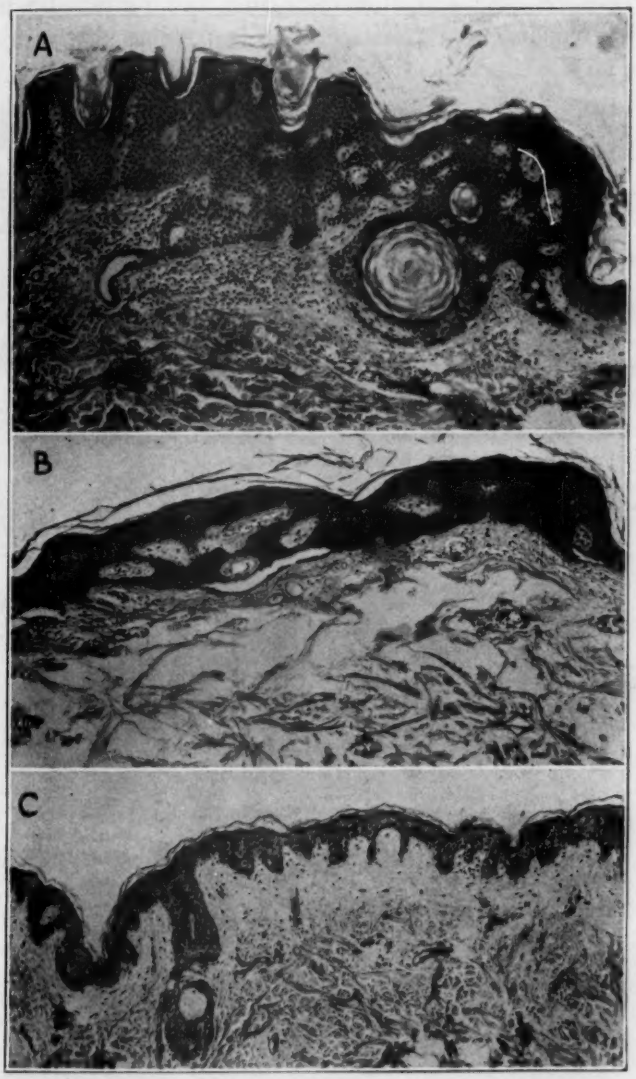

Fig. 2.—*A*, photomicrograph of tissue of keratosis seborrheica before treatment. *B*, tissue similar originally to that of *A*, from the same patient, six months from the beginning of treatment. *C*, skin of the same patient, following thirteen months' treatment, from a site previously occupied by a lesion similar originally to that of *A*.

the remaining 32 subjects improvement of some degree could be seen; either a portion of the total number of lesions in a case disappeared

completely, some lesions persisting, or all lesions regressed, although not completely, or some combination of these two circumstances existed. The degree of improvement in such cases varied from slight to decided, but on the whole was fairly decided if it occurred at all. Occasionally, lesions regressed over several months and then remained unchanged during the remainder of treatment. It is possible that still further

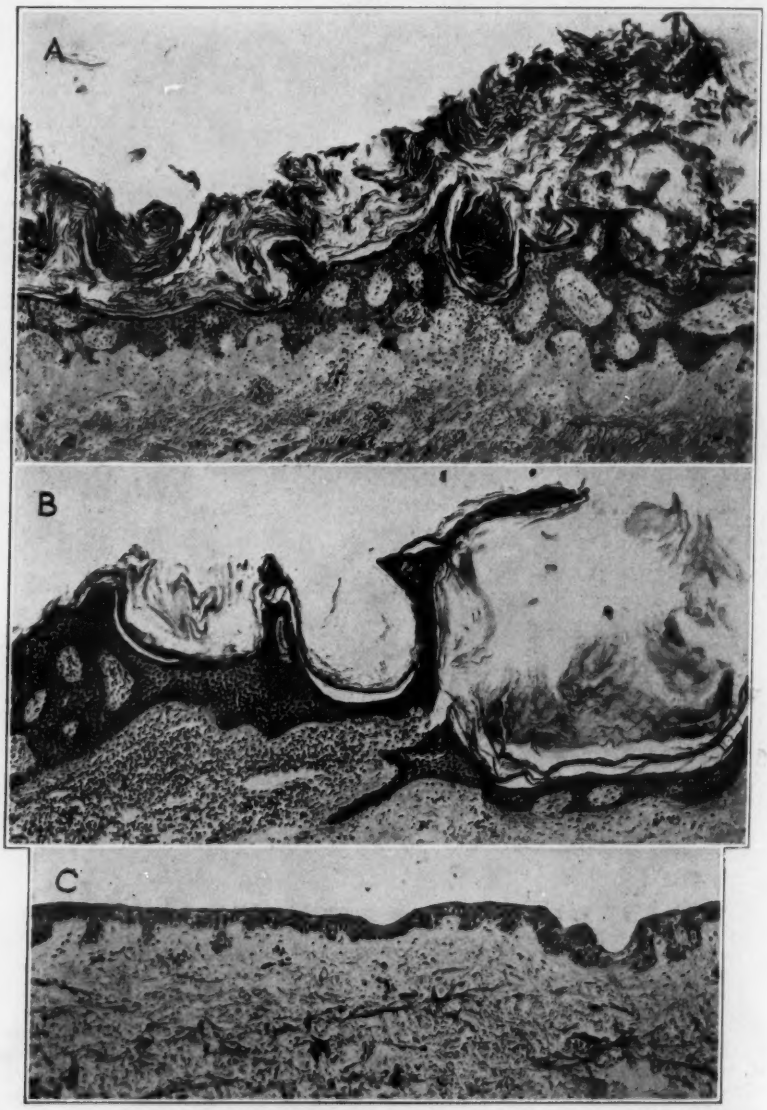

Fig. 3.—*A*, photomicrograph of tissue of keratosis senilis before treatment. *B*, tissue similar originally to that of *A*, from the same patient, after five months' treatment. The lesion had become softer and more translucent. *C*, skin of the same patient, after one year of treatment, from site previously occupied by a lesion of keratosis senilis similar originally to that of *A*.

prolongation of treatment might have resulted in a greater number of subjects all of whose lesions disappeared completely.

Many lesions of keratosis seborrheica were pigmented; when these regressed, the pigment also decreased. Dendritic cells of Langerhans were increased in number particularly in keratosis seborrheica, whether the latter was pigmented or not; the dendritic cells disappeared along with the lesions. In preparations for nerve fibers, the abundance and type of nerve fiber could not be evaluated regularly enough to make possible a conclusion regarding terminal nerve elements in relation to vitamin A deficiency and keratosis seborrheica.

In 1 case it was thought that basophilic degeneration of collagen in the upper part of the dermis was improved somewhat by vitamin A. In a few cases, following treatment, elastic tissue was considered to be in a slightly less frayed and a more abundant condition. In general, however, while keratotic lesions regressed, specifically senile features were unaltered.

Study of a limited number of sections for fat and for vitamin A fluorescence served only to confirm previous observations [5] that no vitamin A is observed in epidermis in either deficiency or overabundance of the vitamin and that the condition of the fat stores is not necessarily relevant to the vitamin A deficiency.[6]

SUMMARY AND CONCLUSIONS

Fifty subjects with keratosis seborrheica and keratosis senilis were given 100,000 units of vitamin A by mouth daily for an average of nineteen and eight-tenths months. In 13 cases all lesions disappeared; in 32 a varying degree of improvement resulted; in 5 no change was observed. No change occurred in a control group of 30. Vitamin A deficiency appears to play some part in the development of keratosis seborrheica and keratosis senilis, but it is not solely responsible. Other factors, including changes of age, must also be considered. Vitamin A deficiency and the intrinsic individual factor appear to be associated in determining the lesion.

Dr. William N. Keller, Superintendent, Western State Hospital, gave his cooperation and encouragement in carrying out the study.

Dr. Jon V. Straumfjord gave advice.

Vitamin A used in the study was supplied by Bioproducts Corporation, Astoria, Ore., through the Astoria Extension Research Laboratory, Department of Biochemistry, University of Oregon Medical School, and the Clinical Studies Foundation, Astoria, Ore.

5. Cornbleet, T., and Popper, H.: Properties of Human Skin Revealed by Fluorescence Microscopy, Arch. Dermat. & Syph. **46**:59-65 (July) 1942.

6. Moult, F. H.: Histopathology of Rat Skin in Avitaminosis A, Arch. Dermat. & Syph. **47**:768-777 (June) 1943.

TUBERCULOSIS MILIARIS DISSEMINATA CHRONICA IN THE NEGRO

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THE TITLE "Tuberculosis Miliaris Disseminata Chronica" is used advisedly instead of "Tuberculosis Miliaris Disseminata Faciei," because the eruption in the Negro, in addition to its facial localization, is present on other parts of the cutaneous surface, and since the lesions persist indefinitely the word "chronica" is appended. This relatively benign disease has been observed only in the adult Negro, and it is to be distinguished from acute miliary tuberculosis with cutaneous manifestations developing in infancy and early childhood, which results from overwhelming infection.

The incidence of tuberculous infection is admittedly greater in Negroes than in white persons,[1] and this applies equally to invasion of the blood stream by the tubercle bacillus with subsequent involvement of the skin.[2] Since tuberculous disease in the Negro is decidedly commoner in young women,[1] it is not surprising to see cutaneous evidences of this disease oftener in this sex. Despite the frequency of tuberculous manifestations of the skin, tuberculosis miliaris disseminata chronica is relatively rare in the Negro when compared with the rather common development of papulonecrotic and micropapular tuberculids. In tuberculosis miliaris disseminata chronica, there is a tendency for concomitant involvement of the internal viscera and the morbidity is usually greater in Negro than in white patients. The observations recorded in this paper are based on a study of 7 histologically proved cases.

The eruption usually commences and is most commonly observed on the face, and it may be limited to this area, but lesions may be seen on any part of the cutaneous surface except the palms and soles. There is a decided tendency for generalization, and patients with eruptions of universal cutaneous distribution have been encountered. The eruption has a predilection for the free margins and both canthi of the eyelids, the alae nasi, the vermilion borders of the lips, the angles of the mouth,

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From the Department of Dermatology and Syphilology of the Harlem Hospital, Dr. Oswald La Rotonda, Medical Director.

1. Lewis, J. H.: The Biology of the Negro, Chicago, University of Chicago Press, 1942, p. 153.
2. Lewis,[1] pp. 141 and 144.

the extensor aspects of the extremities and the oral cavity. It is symmetric and asymptomatic and consists of lesions varying in size from that of a pinpoint to that of a pinhead to that of a match head and, rarely, to that of a pea. They are firm slightly elevated pinkish or reddish brown or brownish closely aggregated discrete papules which may be capped with rough firmly adherent brownish crusts, thickest in the center and gradually thinning toward the periphery. Pinhead-sized papules are the most numerous, and those of rather long duration assume various

Fig. 1.—Facial eruption, showing predilection of lesions for the eyelids and angles of the mouth.

shades of brown. Lesions with crusts may be so prevalent as to dominate the clinical picture.

Papules may coalesce, forming patches of different size and shape, either as linear or, more frequently, as circular configurations which often join with their neighbors to form well marginated irregular slightly infiltrated superficial serpiginous plaques, covered with small firmly adherent whitish scales and/or adherent thin brownish crusts. The serpiginous plaques show partial involution of the central areas. Their margins are slightly elevated, glistening, threadlike and firm, and

here may sometimes be seen discrete closely set pinhead-sized to match head-sized brownish or blackish papules. In the plaque variety, lesions develop in profusion, and careful examination may disclose one or more patches consisting of closely aggregated papules which have not as yet coalesced.

Fig. 2.—Eruption showing generalized cutaneous involvement.

Diascopic pressure discloses a diffuse light brown discoloration, but some lesions show merely blackish pigmentation. As the lesions commence to resolve, they flatten and there is a sinking down of the central area in those containing crusts, the latter falling off shortly afterward. Thin whitish scales may form on the margins of some of the resolving papules. Pinkish areas without sequelae or with atrophic scarring of

different grades, which approximate in size those of the original lesions, appear at sites of complete healing, but they subsequently assume the color of normal skin or, more frequently, become either partially depigmented or hyperpigmented.

The oral eruption is confined chiefly to the hard and soft palates, but lesions have been noted on the buccal mucosa opposite the molars and about the angles of the lips. The lesions correspond to those seen on the skin as regards color, symmetry, grouping and coalescence, but clinical evidence of necrosis has not been observed.

Asymptomatic nonsuppurative involvement of the lymph nodes is relatively common, the posterior cervical, inguinal and mediastinal chains being affected chiefly. Lymph nodes of the former two groups

Fig. 3.—*A*, plaque type of tuberculosis miliaris disseminata chronica. *B*, lesions of the same patient, showing the psoriasiform character of the eruption.

are usually discrete and enlarged to the size of a bean or a hazelnut, and the overlying skin is normal. Splenomegaly may also be detected; in 1 case a smooth firm nontender spleen was palpated 4 fingerbreadths below the costal arch. Besides the enlarged mediastinal lymph nodes, which are identified on roentgenograms by increased root shadows and by widening of the superior mediastinum, the lungs are frequently attacked by way of the circulation. In addition to active tuberculous infiltrations of the usual adult bronchopulmonary type, well defined plaquelike and miliary lesions, similar to those on the skin and scattered throughout both lungs, may be noted in roentgenograms. Roentgenograms of the hands and feet fail to disclose pathologic changes within the bones.

Intracutaneous injections of 0.1 cc. of old tuberculin in a dilution of 1 to 10,000 may provoke a local reaction, but in a dilution of 1 to 1;000 positive reactions of varying intensity usually result. Tubercle bacilli have not been identified in sputum, even though roentgenograms disclose active pulmonary involvement. Hemograms invariably show secondary anemia associated with lymphocytosis and sometimes monocytosis.

Subjective symptoms fluctuate widely. Some patients are asymptomatic, while others have one or more of the following complaints: cough, loss of weight, night sweats, fever, anorexia, hoarseness and painful swelling of both large and small joints. The first four symptoms are associated with pulmonary activity, and there is an associated increase in the pulse and respiratory rates. Coughing is productive of small amounts

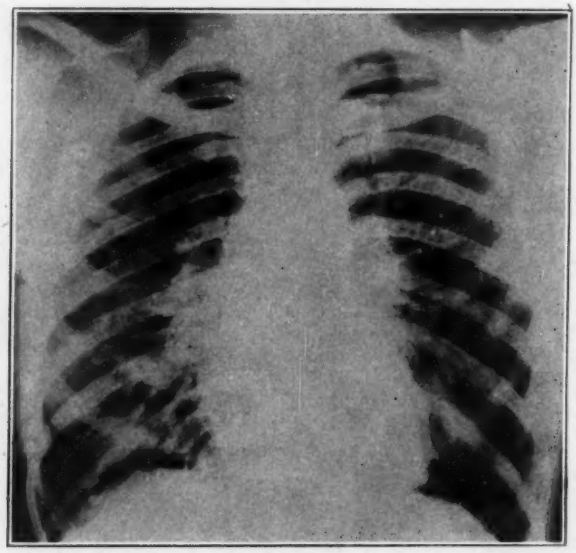

Fig. 4.—Roentgenogram showing pulmonary involvement in the plaque type of eruption.

of yellowish white sputum, which is rarely blood streaked. In 1 case hoarseness was produced by lesions within the larynx. Patients may present asymmetric painful tender swellings of the metatarsal, ankle or knee joints, and while the affected areas feel warm, the skin is nonhyperemic. Furthermore, roentgenograms of the involved joints fail to show pathologic changes, and the symptoms subside entirely within seven to ten days without sequelae.

HISTOLOGIC STUDY

The inflammation may affect the entire skin, extending from the epidermis to the upper levels of the subcutis; the latter layer, however, is involved infrequently. The maximum reaction is centered within the

cutis, particularly within the upper half and most frequently within the upper fourth of this layer. On rare occasions a massive granuloma may occupy the entire middle layer of the skin. The papillae and subpapillae and less often the subpapillae and a small segment of adjacent underlying cutis are the areas most severely affected.

The densely cellular granuloma is well marginated and entirely perivascular and consists principally of closely aggregated foci of miliary epithelioid tubercles. Peripheral and parallel to and below the main infiltrate the tubercles are scattered and appear chiefly as single nodules, the tendency toward grouping being minimal. An occasional edematous epithelioid tubercle surrounded by edematous connective tissue may be noted in both superficial and deep layers of the cutis. Both "naked" and "dressed" tubercles are present within the same section. The latter are the commoner, being enveloped by diverse numbers of small lymphocytes, a few of which are invariably dispersed through the tubercles. Miliary epithelioid tubercles may coalesce, forming either large nodules or diffuse tuberculoid structure. It is not uncommon to see small perivascular collections of epithelioid cells which at times exhibit such great proliferating tendencies as to form large diffuse plaques of tuberculoid structures showing no attempt at tubercle formation. These massive infiltrations of epithelioid cells may be of such degree as to dominate the histologic picture.

Necrotic phenomena are noted frequently, developing invariably within the upper eighth of the cutis and most often within the papillae and subpapillae. These destructive foci vary as to size and shape, and they may be either caseous, liquefaction or coagulation in type, the caseous variety being the commonest and coagulation necrosis the least frequent. It is not unusual to observe two different types of necrosis within the same section, but at different levels.

Multiple small closely grouped or widely separated foci of caseous necrosis, enveloped by edematous connective tissue, develop within the subpapillary layer, at times extending upward for a short distance into the papillae and/or downward for a similar distance into the reticular layer. In a single instance a minute focus of caseous necrosis was observed in the deep part of the cutis.

Liquefaction necrosis, appearing as a single relatively large area, may occur simultaneously with either caseous or coagulation necrosis, lying superficial to the former and below the latter. These destructive foci either border one another or lie a short distance from each other. Coagulation necrosis develops as a single small focus within a papilla; it may be so minute and superficial as to be limited to the papillary tip. Bordering these various necrotic areas are discrete and coalesced miliary epithelioid tubercles and/or diffuse infiltrations of epithelioid cells and Langhans' giant cells.

The number of Langhans' giant cells within sections differ greatly. They may be absent even though the infiltrate is extensive, but as a rule they are seen in moderate numbers. These cells may be detected in any part of the cutis; they may even occupy the summits of the papillae or lie apart from the infiltrate, or they may be noted within tubercles situated in the deep part of the cutis. As many as three Langhans' giant cells were noted within a single tubercle situated in the center of the infiltrate; they are, however, rarely seen in the outlying epithelioid

Fig. 5.—View of an entire section, showing the superficial dense well defined character of the infiltrate.

nodules. These multinucleated cells are also present in small numbers within the diffuse infiltrating epithelioid cell plaques. Giant cells, singly or in small groups, may be detected lying free of the densely cellular infiltrate or surrounded either by a few epithelioid cells or by small numbers of lymphocytes within an edematous stroma. Giant cells were even noted bordering one side of a dilated blood vessel in the middle and deep layers of the cutis; in one section as many as six giant cells were present in such relation to a vascular channel.

The numbers of small lymphocytes vary considerably in sections from different lesions in the same patient. They are usually present in relatively large numbers about the papillary blood vessels. They are distributed unevenly about the tubercles and diffuse infiltrations of epithelioid cells, but they are scarce within these structures. In the outlying areas well defined compact perivascular lymphocytic infiltrates are slight to moderate in degree, and within them may be seen an occasional epithelioid cell and sometimes varying numbers of fibroblasts,

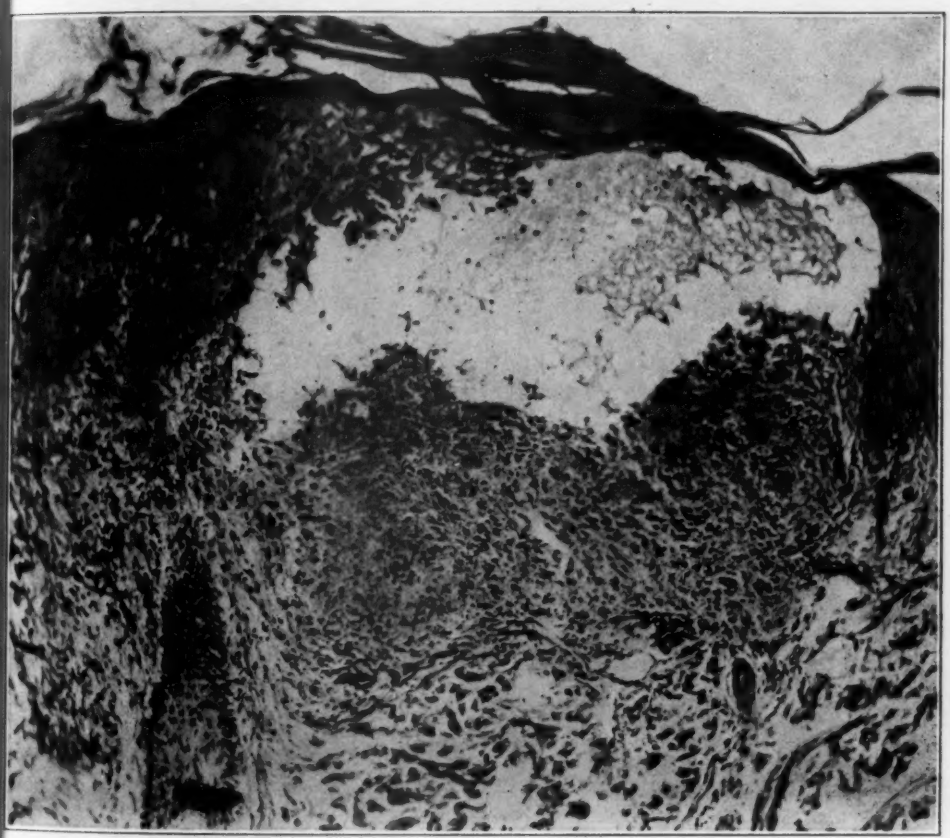

Fig. 6.—Focus of liquefaction necrosis in the superficial part of the cutis and overlying epidermis. The lower border is surrounded by epithelioid tubercles.

depending on the healing tendencies. Throughout the section a few plasma cells may be noted mingling with lymphocytes, but they are more frequent within the papillae. In 1 patient with concomitant syphilitic infection, plasma cells were present in large numbers. In some sections occasional small foci of polymorphonuclear neutrophils with rare polymorphonuclear and mononuclear eosinophils may also be seen.

The blood vessels within the cutis show variable degrees of expansion; some are congested with erythrocytes, and a few are partially thrombosed. Vascular dilatation is most evident in the outlying vessels and minimal within the dense cellular infiltrate. The lining endothelial cells may show either no reaction or mild to moderate degrees of proliferation and swelling. The perivascular connective tissues are usually edematous, and this reaction is rather evident in the tissues beyond the main infiltrate.

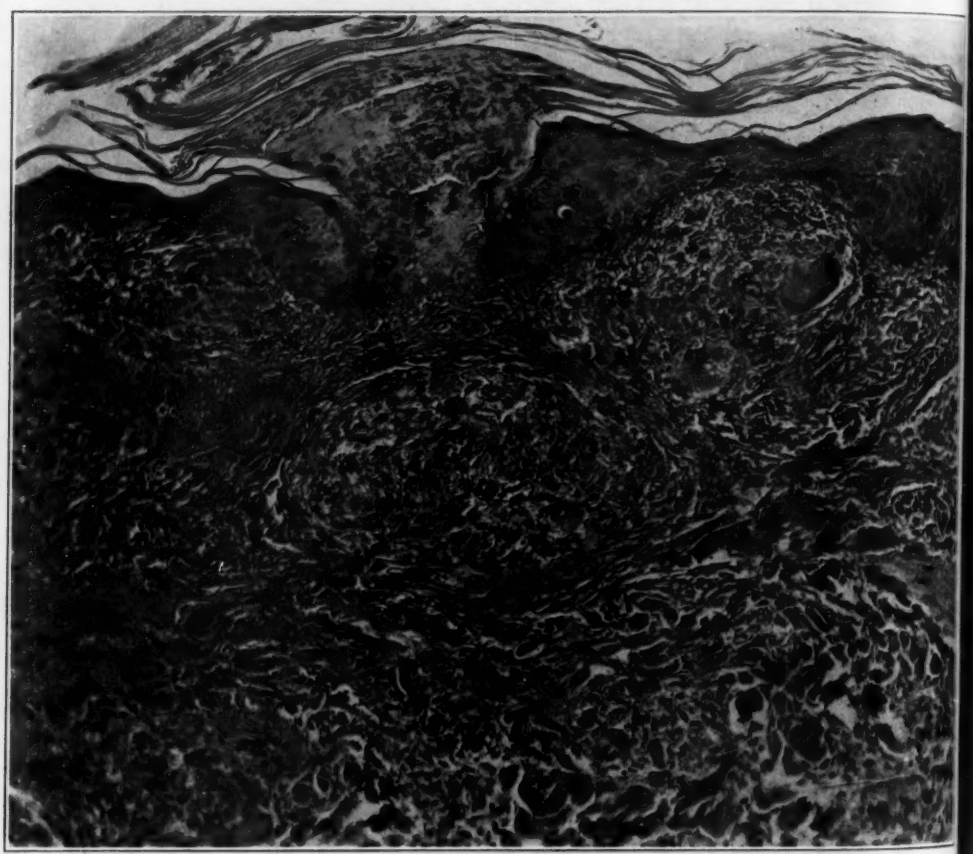

Fig. 7.—Photomicrography showing a small focus of coagulation necrosis in the papilla and overlying epidermis and the sarcoid-like character of the infiltrate.

In the majority of lesions, even those which have persisted for long periods, healing tendencies are either absent or ineffective. Mild fibroblastic reactions are noted about and sometimes within the cellular nodules peripheral to and below the main infiltrates. On rare occasions a lesion may show satisfactory attempts at healing, one or more of the outlying tubercles being replaced by fibrous tissue, and sometimes fibro-

blastic reactions within the diffuse tuberculoid structures are decidedly noticeable. Small deposits of melanin, lying free and within phagocytes, are scattered through the upper part of the cutis, but they are seen chiefly in the papillae and subpapillae; lesser amounts are present within the dense infiltrates and also within the necrotic foci.

On rare occasions the inflammation does attack the subcutis. It is noted within the upper half, but most often within the upper fourth of this layer. The cellular infiltrates and vascular reactions are similar to those observed in the cutis, but develop on a lesser scale. In a single instance one small irregular area of caseous necrosis, enveloped by epithelioid tubercles, was observed in the upper part of the subcutis. Ineffectual attempts at healing were also noted within this layer.

The epidermis overlying the severest inflammatory reactions in the cutis is decidedly irregular, varying from atrophy to normal thickness to mild degrees of hyperplasia and showing either an absence or blunting of the rete pegs or hyperplastic pegs; the latter dip down between and surround the tubercles. Hyperplasia of the rete pegs did not occur whenever necrosis developed within the cutis. Moderate numbers of prickle cells exhibit mild to severe grades of edema, terminating occasionally in vacuolar degeneration and necrosis. Both liquefaction and coagulation necrosis of the epidermis develop directly above similar destructive changes within the papillae, and in their presence the overlying stratum corneum is replaced by a small thick layer of parakeratosis. In the absence of epidermal necrosis the granular layer varies from atrophy to normal thickness and, on occasion, to hyperplasia, the latter as part of a general hyperplastic reaction. The granular cells may also show edematous reactions, but to a lesser extent than those observed in the prickle cells. The stratum corneum shows both hyperkeratosis and parakeratosis, the former predominating and appearing oftenest as dense closely adherent layers. In a few instances densely packed layers of keratin occlude widened follicular orifices. In the severely damaged epidermis the pigment in the basal cells is greatly diminished or absent; decreased amounts may also be observed in the basal cells in areas of general epidermal hyperplasia. Melanin may also be seen at times in the prickle cells and even in the cells of the stratum corneum.

COMMENT AND SUMMARY

The Negro's lack of resistance to tuberculous infection, leading to invasion of the blood stream in a high percentage of cases, is well known. In clinical practice tuberculids in Negro women are familiar diagnostic observations. Nevertheless, despite the frequency of this group of diseases, tuberculosis miliaris disseminata chronica manifests itself rarely.

Negroes exhibit a greater allergic response to tuberculosis infection than do white patients. In tuberculosis miliaris disseminata chronica they

do not display total anergy, as do most white patients, for Negroes react invariably to an intracutaneous injection of 0.1 cc. of old tuberculin in a dilution of 1 to 1,000, and it is not unusual to obtain a positive local reaction with a dilution of 1 to 10,000. On the other hand, tuberculin therapy has limited value. Calciférol (vitamin D_2) therapy does influence favorably the course of the disease in some patients, but prior to its use the eruption was extremely resistant to treatment; in fact, complete resolution of any one lesion was not observed even after an observation period of one year. In white patients the cutaneous lesions have a tendency to heal spontaneously after a variable period.[3]

In the Negro tuberculosis miliaris disseminata chronica has a decided tendency toward generalized cutaneous involvement. Early lesions are pinkish brown or reddish brown, but they lack erythematous areolas. These lesions have a decided tendency to group and, at times, to coalesce, forming scaly and/or crusted patches of different size and shape. In the plaque type the lesions develop in relative abundance, and the central areas of these serpiginous plaques show incomplete healing.

In tuberculosis miliaris disseminata chronica the internal viscera are commonly attacked. The lymph nodes of the posterior cervical chain and those of the mediastinum are affected chiefly, enlarging to a variable degree. The tonsils have been reported involved,[4] and splenomegaly and tuberculous laryngitis were noted in my series. In the presence of generalized eruptions it is not unusual to observe the lungs to be the seat of this disease, the pulmonary lesions often resembling the cutaneous in so far as their discreteness or coalescence is concerned. Furthermore, pulmonary tuberculosis of the adult bronchopulmonary type may also be associated with this disease. These types of pulmonary lesions also develop in white patients.[5]

Histologically, the well defined perivascular inflammatory reaction is centered primarily in the cutis and oftenest in the superficial areas, the epidermis and subcutis being implicated secondarily. In the absence of necrotic processes within the collagen, differentiation from Boeck's sarcoid and micropapular tuberculid may be impossible. In tuberculosis miliaris disseminata chronica the uneven distribution of small lymphocytes about the epithelioid tubercles may have diagnostic significance.

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3. Wile, U. J., in discussion on Foerster, O. H., and Foerster, H. R.: Disseminated Miliary Tuberculosis, Arch. Dermat. & Syph. **15**:364 (March) 1927. Schmidt, F. R., in discussion on Ormsby, O. S.: Lupus Miliaris Disseminatus Faciei, ibid. **30**:290 (Aug.) 1934.

4. Barney, R. E.: Lupus Miliaris Disseminatus Faciei, Arch. Dermat. & Syph. **18**:950 (Dec.) 1928.

5. Zwick, K. G., in discussion on Oliver, E. A., and Finnerud, C. W.: Lupus Miliaris Faciei, Arch. Dermat. & Syph. **15**:610 (May) 1927. Michelson, H. V.: Lupus Miliaris Disseminatus Faciei, ibid. **20**:408 (Sept.) 1929.

The observation of foci of caseous, liquefaction or coagulation necrosis, either singly or as multiple types simultaneously, is characteristic of this disease in the Negro; caseous necrosis is observed most frequently. These necrotic foci are commonly surrounded in part by miliary epithelioid tubercles and/or diffuse tuberculoid structure and Langhans' giant cells. The absence or presence of these giant cells, regardless of number, has no diagnostic value, but their presence in numbers bordering dilated blood vessels has not been encountered in any other type of cutaneous tuberculosis.

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LUPUS ERYTHEMATOSUS PROFUNDUS (KAPOSI-IRGANG)

Historical Review and Report of a Case

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THE BASIC division of lupus erythematosus into the unspecified (or discoid) and disseminated forms, as followed in most textbooks and in the "Standard Nomenclature of Disease and Operations," does not take into account the subcutaneous nodular form which the lesions of this disease may rarely assume.

HISTORICAL BACKGROUND

No mention of this variant of lupus erythematosus is made by Morrow (1894),[1] Shoemaker (1900),[2] Hyde and Montgomery (1904),[3] Stelwagon (1910),[4] Hartzell (1917),[5] Andrews (1938)[6] or Sutton and Sutton (1939).[7] Andrews (1938)[6] did mention sarcoid of Boeck as one of the diseases from which acute disseminated lupus erythematosus might have to be distinguished, but it seems clear that this was not an allusion to a subcutaneous or nodular form of lupus erythematosus. Andrews, in the third edition of his text (1946),[8] referred under the name "lupus erythematosus profundus" to that form of the disease in which a "deep brawny induration beneath a typical discoid patch may extend throughout the thickness of the cheek." This description

1. Morrow, P. A.: A System of Genito-Urinary Diseases, Syphilology and Dermatology, New York, D. Appleton & Company, 1894, vol. 3, pp. 553-562.

2. Shoemaker, J. V.: A Practical Treatise on Diseases of the Skin, ed. 3, New York, D. Appleton & Company, 1900, pp. 587-592.

3. Hyde, J. N., and Montgomery, F. H.: A Practical Treatise on Diseases of the Skin, ed. 7, Philadelphia, Lea Brothers & Company, 1904, pp. 683-693.

4. Stelwagon, H.: Treatise on Diseases of the Skin, ed. 6, Philadelphia, W. B. Saunders Company, 1910, pp. 732-747.

5. Hartzell, M. B.: Diseases of the Skin, Philadelphia, J. B. Lippincott & Company, 1917, pp. 357-367.

6. Andrews, G. C.: Diseases of the Skin, ed. 2, Philadelphia, W. B. Saunders Company, 1938, p. 385.

7. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, pp. 359-372.

8. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 588.

does not fit the cases described and reported by Irgang [9] or the case to be reported herein; it is, however, a reference to deep-seated lesions in this disease. Becker and Obermayer (1940) [10] stated that "certain forms of" sarcoid of Boeck may mimic lupus erythematosus; as in the case of Andrews,[6] however, this seems more likely to be an allusion to the similarity of Besnier's lupus pernio and some cases of disseminated lupus erythematosus than to nodular lesions in the latter disease.

A few authors mentioned this variant of lupus erythematosus in more or less detail. To take them up in reverse chronologic order, as being a more logical sequence, one would begin with Andrews (1946),[8] already mentioned. Ormsby and Montgomery (1943) [11] mentioned lupus erythematosus profundus as having been described by Irgang [9] and Bechet,[12] which is not really correct, since Bechet actually described lupus erythematosus hypertrophicus et profundus, which is a different process both clinically and histologically. They also stated that the lesions resemble Darier-Roussy sarcoid and erythema induratum (which is correct) and "show histologic changes suggestive of sarcoid" (which seems debatable). Jadassohn (1938) [13] listed "erythematodes tumidus" as a rare variant of lupus erythematosus and said that it must be distinguished from sarcoid—a concise and helpful observation.

Pusey (1911),[14] though he described neither superficial nor deep nodular lesions in lupus erythematosus, alluded to Crocker's having described "superficial nodules" as an occasional concomitant of the discoid form of the disease. Crocker himself (1893),[15] like Duhring (1877),[16] credited Moriz Kaposi with the description of "subcutaneous swellings of peculiar character" (Duhring) or "subcutaneous, deeply seated, doughy, painful and tender nut-sized nodules appear[ing] while the skin over them is still normal" (Crocker). Duhring [16] added that he had never encountered such lesions.

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9. Irgang, S.: Lupus Erythematosus Profundus, Arch. Dermat. & Syph. **42**:97 (July) 1940.

10. Becker, S. W., and Obermayer, M.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940, p. 390.

11. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 890.

12. Bechet, P.: Lupus Erythematosus Hypertrophicus et Profundus, Arch. Dermat. & Syph. **45**:33 (Jan.) 1942.

13. Jadassohn, J.: Dermatologie, Berlin, Weidmann & Company, 1938, pp. 631 and 634.

14. Pusey, W. A.: Principles and Practice of Dermatology, ed. 2, New York, D. Appleton & Company, 1911, pp. 373-383.

15. Crocker, H. R.: Diseases of the Skin, ed. 2, Philadelphia, P. Blakiston, Son & Company, 1893, p. 531.

16. Duhring, L. A.: A Practical Treatise on Diseases of the Skin, ed. 1, Philadelphia, J. B. Lippincott & Company, 1877, p. 416.

The section on lupus erythematosus in Kaposi's textbook, in both the second edition (1883) [17] and the fifth edition (1899),[18] contains one paragraph (the same in both editions) which appears to be concerned with nodular or deep-seated lesions of lupus erythematosus. It reads as follows: "Thus the process begins at one time in the upper layers and in the neighborhood of the blood vessels surrounding the sebaceous glands and their ducts (red, elevated macules), and at another time in the deep [layers], in the neighborhood of the vascular network belonging to the sweat glands and the fat lobules (firm, edematous nodules), and spreads throughout all the skin layers and tissues." A little later, after describing the essential histologic features of the infiltrate, he says again that it may occur "either in the deep part of the corium (nodules) or in the superficial layers (red macules)." (The words in parentheses are in all cases his own, not mine.) Despite the casualness of Kaposi's references to deep-seated nodular lesions in lupus erythematosus, no illustration of this variant of the disease is included among the twelve plates of lupus erythematosus (including the discoid, disseminated and bullous varieties) in his "Handatlas der Hautkrankheiten," [19] published in 1898.

Irgang's review and report of a case in 1940 [9] seems to be the first definitive presentation of lupus erythematosus profundus in the American literature. Like Oppenheim,[20] Irgang credited Brocq (1895) [21] with the original description of the disease. However, Brocq's article consists entirely of an argument for tuberculosis as the cause of those forms of lupus erythematosus situated on the head, unilaterally or at least asymmetrically, and characterized by "depth, fixity, and gradual evolution." Obviously lupus erythematosus profundus would fit perfectly into such a category; so, however, would lupus erythematosus hypertrophicus (et profundus) and many a case of so-called "fixed" chronic discoid lupus erythematosus. As an original description of lupus erythematosus profundus it hardly seems adequate. In any event, it is antedated nearly twenty years by the second edition of Kaposi's work.

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17. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, ed. 2, Vienna, Urban & Schwarzenberg, 1883, p. 642.

18. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, ed. 5, Berlin, Urban & Schwarzenberg, 1899, p. 749.

19. Kaposi, M.: Handatlas der Hautkrankheiten, Vienna, Wilhelm Braumüller, 1898.

20. Oppenheim, M.: Lupus erythematosus profundus, Arch. f. Dermat. u. Syph. **115**:847, 1913.

21. Brocq, L.: Sur la nature du lupus érythémateux, Rév. gén. de clin. et de thérap. **9**:113 (Feb. 23) 1895.

Pautrier's article on lupus erythematosus [22] in the 1936 edition of the "Nouvelle pratique dermatologique" throws considerable light on the question of whether Brocq first described lupus erythematosus profundus. He said that during the twelve years he worked at Brocq's side this deep variant of lupus erythematosus was not mentioned, nor did he see an example of it. He then cited a passage from Brocq's "Elementary Treatise on Dermatologic Practice," which indicates that Brocq believed that *lupus érythémateux profond* should be classified with tuberculous lupus (cf. the previous reference to Brocq [21]) and, even more important for our present purposes, that the disorder so designated was "characterized by an external appearance of lupus erythematosus (speckled redness [*rougeur, piqueté*] and whitish areas [*tractus blanchâtres*]) and by a deep, almost cartilaginous infiltration of the integument." It seems clear from this that *lupus érythémateux profond de Brocq* was what would now be called "lupus erythematosus hypertrophicus et profundus (Bechet)" and that there is no reason to suppose that Brocq ever described that variant of the disease which is now called "lupus erythematosus profundus (Kaposi-Irgang)."

CLINICAL FEATURES

Irgang's report [9] clearly defined the essential features of lupus erythematosus profundus. Ordinary discoid lupus erythematosus is usually also present. The patient presents, in addition, one or more firm, sharply outlined, movable subcutaneous nodules or tumors, with normal-looking overlying skin. Clinically, these lesions are identical with those of Darier-Roussy sarcoid.[23] Histologically, they consist of a compact periglandular and perivascular lymphocytic infiltrate, with a few histiocytes and plasma cells and sometimes some polymorphonuclear leukocytes and thickening of blood vessel walls. The picture is not at all that of sarcoidosis. The overlying epidermis usually shows microscopic follicular plugging. In Irgang's case, as in the case to be reported here, no necrosis was noted and no acid-fast bacilli were seen.

Irgang's patient was hypersensitive to tuberculin; the intradermal injection of 0.1 cc. of a solution of old tuberculin in dilution of 1 to 100,000 produced a severe reaction lasting six weeks, and a positive reaction was obtained with the same dose in a dilution of 1 to 1,000,000,000,000,000 Treatment with intramuscular injections of bismuth subsalicylate, intravenous injections of gold sodium thiosulfate and desensitization to tuberculin resulted in a cure. Irgang concluded

22. Pautrier, L. M.: Lupus erythematosus, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 3, p. 747.

23. Darier, J., and Roussy, G.: Des sarcoïdes sous-cutanées, Arch. de méd. exper. et d'anat. path. **18**:1, 1906.

that the lesions in her case, and probably also in other cases, were caused by tuberculosis.

Irgang reviewed the periodical literature in detail and demonstrated the remarkable confusion, particularly with relation to various types of sarcoid, that had regularly clouded the diagnosis of lupus erythematosus profundus. Because of this confusion, because of the rarity of the disorder and because of the apparent success with which it may be treated, this example of lupus erythematosus profundus is reported.

REPORT OF CASE

H. Y., a 45 year old Japanese housewife, was first seen in November 1945, because of symmetric slowly enlarging facial tumors of four or five months'

Fig. 1.—*A*, symmetric malar lesions of lupus erythematosus profundus. *B*, cicatricial alopecia, the result of a previous attack of discoid lupus erythematosus confined to the scalp.

duration. These were painless, nontender, rubbery-hard, sharply outlined, movable subepidermal masses, measuring roughly 3 by 4 by 5 cm. and situated in the zygomatic areas (fig. 1 *A*). The overlying skin was also movable, though not freely so, and was normal in appearance and texture. The scalp showed numerous scars suggestive of lupus erythematosus (fig. 1 *B*), and it was learned that she had been successfully treated for this disease two years before with intramuscular injections of bismuth subsalicylate in oil. A tentative diagnosis of either lupus erythematosus profundus or Darier-Roussy sarcoid was made.

Biopsy disclosed dilatation and keratinous plugging of the hair follicles (fig. 2 *A*); the epidermis and superficial portion of the corium were otherwise normal

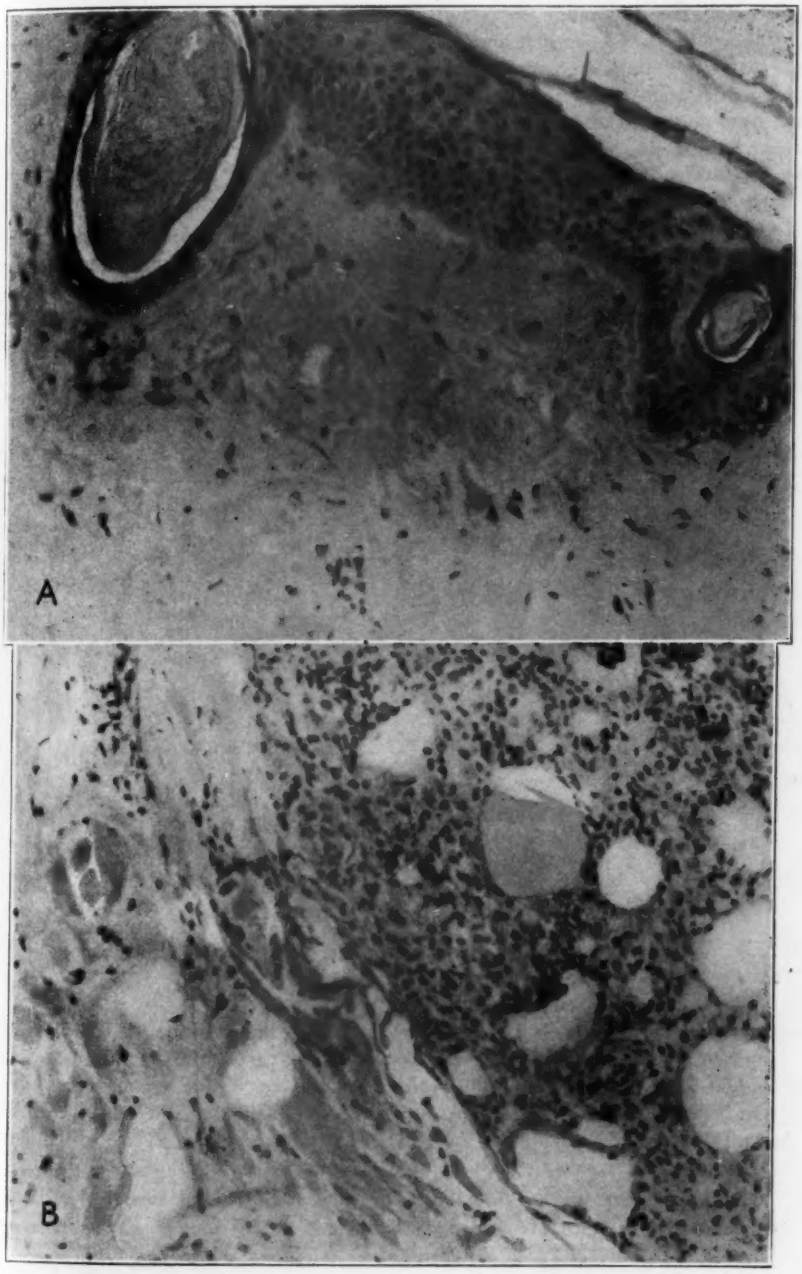

Fig. 2.—*A*, epidermis and upper part of the corium, showing slight disorganization of the basal layer of the epidermis and microscopic dilatation and keratinous plugging of two adjacent hair follicles (hematoxylin and eosin × about 272). *B*, microscopic appearance of cellular infiltrate deep in the corium, showing the sharply defined border which was characteristic (hematoxylin and eosin × about 149).

in appearance except for the mild degenerative connective tissue changes to be expected in the skin of the cheek and a small amount of lymphocytic perivascular cuffing. Deep in the corium and extending into the fat lobules of the hypoderm was a sharply outlined lymphocytic infiltrate, with an admixture of histiocytes and plasma cells and a few polymorphonuclear leukocytes (fig. 2*B*). Fat cells had been destroyed and partially replaced by scar tissue; several small arterioles showed thickening of their walls. The histiocytes were not nearly numerous enough to constitute epithelioid cell tubercles and thus justify a diagnosis of Darier-Roussy sarcoid.

Reactions in serologic tests for syphilis (Kolmer-Wassermann and Eagle) were negative; the hemogram revealed no abnormalities, serum proteins were 7.08 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 2.1 to 1, and the Weltmann coagulation band was 7 (slight right shift, suggesting fibrotic rather than exudative disease). Roentgenograms of the hands, feet and chest

Fig. 3.—Lesions greatly reduced in size after twelve weekly intravenous injections of gold sodium thiosulfate.

revealed no abnormalities. A first-test-strength intradermal dose (0.00002 mg.) of purified protein derivative of tuberculin elicited no reaction; a second-test-strength dose (0.005 mg.) elicited a weakly positive reaction (erythema and elevation about 8 mm. in diameter). Reactions in tests with old tuberculin (0.1 cc. given intradermally) were positive with a 1 to 1,000 dilution (erythema 2 cm. in diameter, with elevation), but negative with 1 to 10,000 and higher dilutions.

The patient was sent to her family physician, Dr. Kinoshi Inouye, for weekly intramuscular injections of bismuth subsalicylate in oil, 0.2 Gm. each. A month after a series of twelve such injections, the lesions were perhaps slightly flatter, but otherwise unaltered, and the medication was changed to weekly intravenous injections of gold sodium thiosulfate. The initial dose was 5 mg., and it was gradually increased so that the eleventh and subsequent doses were 100 mg. No untoward reaction occurred, and after the twelfth dose the lesions were observed to have been reduced from their original size to approximately 0.5 by 1 by 1.5 cm.

(fig. 3). The Weltmann coagulation band was still 7.0, and the hemogram was still normal. The last injection of gold compound was given Sept. 24, 1946, and on October 7 the only discernible residuum of the lesions was slight diffuse thickening of the subcutaneous tissues.

COMMENT

When ordinary discoid lupus erythematosus precedes or accompanies the deep variety of the disease, it provides a useful clue to the correct diagnosis and carries some weight in the corroboration. When this is not the case, the ingenuity and resourcefulness of the physician will really be taxed in arriving at a correct diagnosis.

It does not appear that histologic differentiation from sarcoid is likely to be at all difficult, though clinically the lesions are exactly like those originally described by Darier and Roussy.[28]

SUMMARY AND CONCLUSIONS

Moriz Kaposi described deep subcutaneous lesions of lupus erythematosus in 1883 and was credited by Adolphus Duhring with having described them prior to 1877.

Such lesions are rare and have often been mistaken for Darier-Roussy sarcoid, Boeck's sarcoid or even so-called Spiegler-Fendt sarcoid.

A case of lupus erythematosus profundus is reported, in which hypersensitivity to tuberculin was not present, in which bismuth subsalicylate administered intramuscularly proved ineffective and in which gold sodium thiosulfate given intravenously proved therapeutically effective.

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URTICARIA CAUSED BY HEAT, EXERTION AND EXCITEMENT

Report on Twenty-Two Cases Among American Soldiers in Japan

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URTICARIA caused by heat, exertion and excitement is an uncommon dermatologic disease. The subject is covered only by a phrase or a sentence in such standard textbooks as those of Andrews,[1] Sutton and Sutton[2] and Ormsby and Montgomery[3] under the general heading of "urticaria." Duke,[4] who has pioneered the study of physical allergy, described the first case of urticaria due to heat and exertion in 1924 and proposed the name of "urticaria calorica" for this eruption. Hopkins, Kesten and Hazel[5] reported observations on 15 patients, but did not discuss the incidence of this entity.

Of the 22 cases herein reported, 3 patients were seen on the dermatologic service of the Three Hundred and Sixty-Fourth Station Hospital in Kyoto, Japan, between Dec. 5, 1945 and Feb. 18, 1946. The other 19 were seen between the latter date and June 5, at the Thirteenth General Hospital in Osaka, Japan. During the same periods, 154 new patients with dermatologic disease were seen at the former hospital and 829 were seen at the latter hospital, giving a total of 983 new patients with dermatologic disease with 2.2 per cent of them having this type of urticaria.

Besides these I saw 4 ambulatory patients in the clinic who were not completely studied and were not included in this series. In addition more patients presenting this type of eruption were described to me by a number of dispensary officers of small outlying installations,

1. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1946, p. 168.

2. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935, p. 163.

3. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 150.

4. Duke, W. W.: Urticaria Caused Specifically by Physical Agents, J. A. M. A. **83**:3 (July 5) 1924.

5. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679 (Nov.) 1938.

who treated them symptomatically and lost sight of them for one reason or another. It became apparent that this uncommon eruption was appearing with unusual frequency.

Little seems to be known about the pathogenesis of sensitivity to heat. Duke [6] stated that it "seems to be due to a defect in the heat-regulating mechanism caused commonly by a febrile condition." He also listed other possible causes, as skull fractures, brain hemorrhage, lightning stroke, cardiac or vascular disease, endocrine diseases, intestinal diseases which alter the absorption of histamine-like bodies or diseases which interfere with normal body moisture. He observed a number of patients to be highly sensitive in testing with "infinitesimal amounts" of histamine and stated that the absorption of histamine should theoretically add to the severity of symptoms. Hopkins [5] and his co-workers concluded that whatever the primary stimulus might be, whether heat, exertion or excitement, the attacks are due to the "reaction of cutaneous cells to acetylcholine or closely related compounds."

CLINICAL STUDIES

In this study, besides making clinical observations, an attempt was made to correlate the onset of symptoms with climatic changes and also to study the etiologic and therapeutic relationship of histamine and the disease.

Onset of Symptoms.—In all but 3 patients the onset of symptoms occurred in Japan after they had served the previous summer in the Philippine Islands or in Florida. Also to be noted was the fact they all arrived in Japan in September or October, during the cool autumn months. Since the Philippine Islands and Florida are known to have year round hot weather, especially so in the summer, and since the patients were moved rather abruptly to Japan, which usually has a temperate climate, especially in the autumn when it was decidedly cool, it seems reasonable to assume that this change in climate was of etiologic significance. However the onset of symptoms did not always occur soon after the change in climate took place, but varied from almost immediately to six months later. In 3 patients the symptoms started before they left the Philippine Islands, and a history of climatic changes while there could not be elicited.

Clinical Manifestations.—Symptoms were readily produced by vigorous exertion, any form of external heat or any form of excitement. The patients described rapid development of a generalized itching or

6. Duke, W. W.: Clinical Manifestation of Heat and Effort Sensitiveness and Cold Sensitiveness (Relationship to Heat Prostration, Effort Syndrome, Asthma, Urticaria, Dermatoses, Non-Infectious Coryza and Infections), J. Allergy **3**:257 (March) 1932.

prickling and burning sensation, which was intensely uncomfortable and caused them to scratch and rub their skin. They were impelled to remove some of their clothes or find a cool place, which would relieve them of their symptoms within a few minutes.

During remissions from attacks the patients had apparently normal skin with the exception of 2 patients, 1 of whom had coincidental scabies and the other mild trichophytosis. General physical examination revealed no changes except that 2 patients had intestinal trichuriasis. The attacks of urticaria in these 4 patients persisted long after the coexisting diseases had been cleared up and were apparently not caused by them.

During attacks the eruption developed in groups of flesh-colored to bright red pinhead-sized papules and wheals. Erythema was not always associated with the wheals. The nonerythematous lesions were sometimes difficult to make out, and close examination would be necessary in order to see them. The distribution of the lesions was generalized, involving even the scalp, palms and soles. The most frequent sites of involvement were the shoulders, back and arms. Sometimes "chills" and "shakes" accompanied the sudden onset of severe pruritus.

The skin of all the patients seemed to be of normal warmth to the touch, nor did they appear to have dry skin. However, a number of patients complained of an inability to sweat from areas of glabrous skin, although profuse sweating was observed from the intertrigenous areas, scalp, palms and soles.

Dermographism, although present in all patients was not severe in any of them, and in no patient was it graded more than 3 plus on a scale of 1 to 4 plus.

Allergic History.—The patients, as a group, showed a low incidence of allergic history, either their own or family history. Four patients had previously had an allergic disease, 1 of whom also experienced sensitivity to cold, while 6 had some family history of allergy.

Laboratory Observations.—Laboratory examinations revealed no abnormalities of blood or urine. Eosinophilia was not seen in any patients. Two patients had stools positive for Trichuris trichuria.

Histamine Studies.—Each of the patients was given an intradermal test dose of 0.1 cc. of histamine phosphate in a dilution of 1 to 1,000. There were no systemic reactions from this, and the local wheal produced by the injection at the height of reactivity was large, but not excessively so (average ½ by ¾ inch [1.27 by 1.9 cm.]). Six control patients with nonallergic cutaneous diseases were similarly tested, and wheals which were almost as large (average ⅜ by ⅝ inch [about 1 cm. by 1.6 cm.]) were seen to develop. The difference in average size

of the wheals in the two groups of cases was considered within the margin of error, and it was felt that the patients with sensitivity to heat were not sensitive to histamine.

Horton [7] and, later, Alford and Whitehouse [8] demonstrated that in patients with histamine cephalalgia complicated by duodenal ulcers there was a rise in gastric acidity at the time of the headache, comparable to the rise in gastric acidity produced by an injection of histamine. Analogously, it was felt that if the urticaria in heat-sensitive patients was due to an abnormal release of histamine, there should be a rise in gastric acidity at the time of the development of urticaria. With this in mind gastric analyses for 8 patients were done. The first specimens were taken in a cool room and later specimens in a warm room during the development of urticaria. However, the results were disappointing, since no definite sustained increase in acidity was produced in a hot room after urticaria was induced. This was further confirmed by gastric analyses of 3 control patients, specimens from whom were taken in a cool room and later in a hot room. Studies revealed that their gastric acidity curves corresponded closely to those of the patients with urticaria.

Psychiatric Studies.—Six of the patients were chosen at random for psychiatric examination in order to exhaust the possibility of psychosomatic manifestations, and no evidence of psychic disturbance was observed.

TREATMENT

Systemic Treatment.—The first 3 patients received subcutaneous injections to induce histamine desensitization and seemed to be improved by it. However, histamine desensitization was not as successful in the succeeding patients, and it even appeared questionable whether it was at all effective. The last 4 patients received no histamine. Three of these received only autohemotherapy, while in the last patient the disease was so mild that no treatment was considered necessary. In the few patients that received intradermal or intravenous injections of histamine, no advantage appeared to be obtained. In 1 patient severe headaches and cardiac palpitation began to develop when the dose of histamine in subcutaneous injection reached 0.2 cc. in a dilution of 1 to 1,000, and the treatments had to be discontinued.

Of the 18 patients receiving injections for desensitization to histamine, 8 were improved and 10 unimproved. Of those improved (i.e.,

7. Horton, B. T.: Histamine Cephalalgia Resulting in Production of Acute Duodenal Ulcer, J. A. M. A. **122**:59 (May 1) 1943.

8. Alford, R. I., and Whitehouse, F. R.: Histamine Cephalagia with Duodenal Ulcer, Ann. Allergy **3**:201 (May-June) 1945.

able to return to duty), several still had mild attacks. It was felt that some of the remainder could be expected to have recurrence of symptoms, since a number of patients in the unimproved group had also previously returned to duty and later had to be readmitted.

The effect of epinephrine was interesting in that it did not hasten relief of symptoms nor did it prevent attacks when given a few minutes before the patient was exposed to heat.

Eight patients received autohemotherapy, and although 3 of these were improved the improvement might have been spontaneous, since their symptoms originally were mild. Improvement occurred in most of the patients with mild to moderate disease, regardless of the form of treatment, while most of the patients with severe disease remained unimproved with similar treatment.

Local Treatment.—Any cooling agent would give relief from symptoms. Exposure to cool air, removal of clothes and application of calamine lotion, alcohol or ether were effective. Between attacks the patients remained comfortable as long as they stayed in a cool room or wore light clothing. During the winter months this was a problem, as they insisted on leaving their windows wide open and would stay in bed stripped to the waist. They were unable to wear woolen bathrobes and had to be furnished with white cotton laboratory gowns.

REPORT OF A CASE

A 19 year old soldier was well until November 1945, five months prior to admission, when for the first time he began to experience episodes of intense burning over his body, associated with the appearance of "small bumps." The attacks were brought on by heat, exertion or excitement. Being in a warm room, wearing warm clothes or mild exertion would cause an attack. A sharp command, an exciting movie or a game of cards would also precipitate symptoms.

The onset occurred about a month after he landed in Japan. The patient had previously been stationed in the Philippine Islands.

There was no past personal or family history of hay fever, rose fever, asthma, hives or other allergic diseases.

Physical examination revealed the skin to be apparently normal. There was dermographism of 2 plus. After moderately exercising by bending at the waist for several minutes the patient began to feel burning and itching all over his body. Examination at this time revealed streaks and plaques of erythema scattered on the arms, chest, abdomen, and back. Pinhead-sized wheals appeared on these erythematous areas. However, similar lesions could be seen, with careful observation, on nonerythematous areas. Some of them could actually be seen while they developed. The dermatitis disappeared about ten minutes after the patient cooled off.

Laboratory examination showed erythrocytes 4,500,000, hemoglobin 85 per cent and leukocytes 5,400, with 63 per cent polymorphonuclear cells, 34 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. Urinalysis revealed no abnormality. The Kahn reaction was negative. Stools were negative for ova.

The intradermal test for histamine at the height of reaction produced a wheal ⅝ by ½ inch (about 1.6 by 1.3 cm.).

Gastric analyses at fifteen minute intervals were reported as follows:

In a Cool Room		In a Warm Room	
Total Acid (Degrees)	Free Hydrochloric Acid (Degrees)	Total Acid (Degrees)	Free Hydrochloric Acid (Degrees)
43	28	58	46
52	37	61	48
62	52	63	50
		58	47
		53	41
		62	42

The patient had received ⅜ grain (25 mg.) ephedrine sulfate and ½ grain (30 mg.) phenobarbital prior to admission, without relief. In the hospital calcium gluconate and ammonium chloride were ineffective. Treatment toward histamine desensitization was started but had to be discontinued because of severe headaches and cardiac palpitation, which developed after the dose was increased to 2 cc. in a dilution of 1 to 1,000. Autohemotherapy of 10 cc. of blood was then given intramuscularly three times a week, without amelioration of attacks. The patient was relieved only with coolness and cooling applications.

Evacuation to the zone of the interior was recommended.

SUMMARY AND CONCLUSIONS

Twenty-two patients with urticaria caused by heat, exertion and excitement were observed among American soldiers in Japan. The large number seen here is considered to be unusual. Before arriving in Japan, which is in the temperate zone and is decidedly cool in the autumn, all the patients (except the one from Florida) had spent the previous summer months in the Philippine Islands, where the weather is hot. This represented a rather abrupt drop in climatic temperature of their environment and is probably of etiologic significance except in the 3 patients who already had symptoms before leaving the Philippine Islands.

The eruption was characterized by pinhead-sized wheals, with or without erythema, and accompanied with urgent itching, prickling and burning sensations. Intradermal tests with histamine phosphate in a dilution of 1 to 1,000 showed no evidence of histamine sensitivity. Gastric analyses before and during attacks showed no evidence of abnormal production of histamine.

Treatment in general was unsatisfactory. Histamine phosphate desensitization seemed to be of some value in a few cases. Symptoms could be relieved with any cooling agent. Patients with milder symptoms improved with any form of treatment, while most of the patients with severe symptoms remained resistant to treatment.

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EPIDERMAL ABSORPTION OF DRUGS

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CERTAIN glycols of the ethylene series are absorbable when applied on the intact skin by gentle spreading. This has suggested the possibility of the use of one of these glycols alone or in mixture with other agents, as a vehicle or carrier for drugs, to promote or enhance their percutaneous absorption. One of the glycol derivatives, namely, the diethylene glycol monoethyl ether ("carbitol"), whose toxicity and other effects have been extensively studied in our department appeared suitable for this purpose, since it is both miscible with water and organic solvents, being itself a fairly good solvent for many drugs and, when applied repeatedly to the skin of rabbits, possesses a relatively low degree of systemic toxicity and local irritation.[1] "Carbitol" and several glycols have already been tried in attempts to promote the percutaneous absorption of insulin, with alleged success,[2] but this has not been confirmed by Bruger and Flexner.[3]

This report presents a summary of positive results with selected drugs in "carbitol" alone and in mixture with other vehicles and failures with some other drugs whose absorption might be desired.

METHOD

Unanesthetized rabbits were used in the majority of the experiments. One or two days before the application of the drug the hair of the

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1. Hanzlik, P. J.; Luduena, F. P.; Lawrence, W. S., and Hanzlik, H.: Acute Toxicity and General Systemic Action of Diethylene Glycol Monoethyl Ether (Carbitol), J. Indust. Hyg. & Toxicol. **29**:190, 1947. Hanzlik, P. J.; Lawrence, W. S.; Fellows, J. K.; Luduena, F. P., and Laqueur, G. L.: Epidermal Application of Diethylene Glycol Monoethyl Ether (Carbitol) and Some Other Glycols, ibid. **29**:325, 1947.

2. Major, R. H.: Insulin Absorption from Application to the Skin, Proc. Soc. Exper. Biol. & Med. **34**:775, 1936.

3. Bruger, M., and Flexner, J.: Integrity of the Skin in Relation to Cutaneous Absorption of Insulin, Proc. Soc. Exper. Biol. & Med. **35**:429, 1936.

abdomen was removed with an electric clipper. The solution containing the drug was applied on the clipped area of about 100 sq. cm., being spread gently with a light glass rod, at intervals during one hour, with the animal tied down to a board. The skin was left uncovered, even after removal of the animal to a cage. In a few experiments the animals were anesthetized for carrying out special procedures. Solutions and ointments containing penicillin were also applied on the skin of human volunteers. The type of solution, the methods for estimating the degree of absorption and the results are described separately for each drug grouped according to pharmacodynamic type.

Vehicles Used.—Diethylene glycol monoethyl ether ("carbitol") was used, either alone or mixed with octyl alcohol, in the majority of experiments. Insulin hydrochloride, epinephrine hydrochloride, acetyl-β-methylcholine chloride ("mecholyl chloride"), sodium penicillin and di-hydro-β-erythroidine hydrochloride were soluble in "carbitol"; epinephrine base was not.

Propylene glycol was used alone or mixed with octyl alcohol as a vehicle for epinephrine hydrochloride. Chemically, the octyl alcohol used was the n-hexyl-methyl-carbinol. None of the drugs used by us was soluble in octyl alcohol alone, at least not in the concentration desired. Therefore, they were first dissolved in "carbitol," propylene glycol or ethyl alcohol before the octyl alcohol was added. The proportion of octyl alcohol was usually 1 to 1 of the other solvent, although in a few cases the proportion of octyl alcohol was lower.

Benzyl alcohol was used in two experiments, mixed with "carbitol" as a vehicle for epinephrine.

Herrmann, Sulzberger and Baer [4] developed a penetrating vehicle containing xylene, antipyrine, propylene glycol and an aerosol, for which they coined the generic term "penetrasol." Penetrasol prepared with "aerosol MA" (dihexyl sodium sulfosuccinate) and "aerosol IB" (dibutyl sodium sulfosuccinate) were observed by them to promote the absorption of certain drugs through the skin of human beings and animals. We prepared a mixture according to the method of Herrmann, Sulzberger and Baer,[4] but used another aerosol, i. e., "aerosol OT" (dioctyl sodium sulfosuccinate), with similar general properties. Preliminary trials with this aerosol mixture and large doses of epinephrine (in 2 rabbits) and of crystalline zinc insulin (in 4 rabbits) gave a positive result in 1 rabbit with epinephrine and entirely negative results in the rabbits with insulin. Application of the "aerosol OT" mixture alone to the skin of normal rabbits, in doses of 2 cc. per kilogram, caused some local irritation, as indicated by scattered spots of capillary hemor-

4. Herrmann, F.; Sulzberger, M. B., and Baer, R. L.: New Penetrating Vehicles and Solvents, Science **96**:451, 1942.

rhages and subcutaneous edema. After application for one hour the intravenous injection of 1 per cent solution of trypan blue (0.5 cc. per kilogram) revealed an increased capillary permeability. That is, there was a blue arborescent pattern on the skin and the dye appeared in the gelatinous subcutaneous edema. In other words, this mixture injured the skin and appeared unpromising. It should be added that the aerosols used by Herrmann and his associates were not available to us and that the aerosol used by us was also found ineffective by them.[5] We did not try the milder and later types of vehicles developed by Herrmann,[5] but confined ourselves to vehicles which appeared promising and unobjectionable according to our experience.

SYMPATHOMIMETIC AMINES

Epinephrine.—Epinephrine, which is ordinarily not readily absorbable from body surfaces, was convenient for determining the effects of various vehicles on epidermal penetration. The criteria of absorption used were local vasoconstriction and an increase in the level of sugar in the blood. In all experiments, epinephrine base (supplied by Winthrop Chemical Co., Rensselaer, N. Y.) was used, but since this was not soluble in "carbitol," octyl alcohol or benzyl alcohol, 0.1 or 0.2 cc. of 10 per cent hydrochloric acid was added to the suspension of epinephrine base, with prompt solution of epinephrine hydrochloride. Samples of blood were taken from the ear or saphenous vein before epidermal application and two to five hours afterward, the sugar in the blood being determined by the method of Folin and Malmros.[6] The individual results, with the proportions of the solvents in the various mixtures, are presented in table 1. Results with epinephrine hydrochloride in aqueous solution have been omitted from this table, since they were all negative.

It is seen that only the mixtures containing octyl alcohol promoted satisfactorily the absorption of epinephrine up to a level which produced definite and sustained hyperglycemia. With certain mixtures hyperglycemia was demonstrable for over five hours after application. Epinephrine in "carbitol," propylene glycol, ethylene glycol or in the mixture of benzyl alcohol and "carbitol" was poorly absorbed, producing only a moderate or slight degree of local vasoconstriction and no changes, or insignificant ones, in the level of sugar in the blood. These vehicles alone produced either no effect or only fleeting hyperemia when applied in the same way on the clipped skin, thus indicating their relative noninjuriousness.

5. Herrmann, F.: Personal communication to Dr. Howard Fox, referred to us.

6. Folin, O., and Malmros, H.: An Improved Form of Folin's MicroMethod for Blood Sugar Determinations, J. Biol. Chem. **83**:115, 1929.

It seemed that octyl alcohol was largely responsible for the absorption of the epinephrine. The mixture of octyl alcohol and "carbitol" was as effective as the mixtures of octyl alcohol with propylene glycol and octyl alcohol with ethyl alcohol, and it was less injurious to the

TABLE 1.—*Effects of Epinephrine Applied Epidermally in Rabbits*

Number of Animals	Dose, Mg. per Kg.*	Concentration, %	Vehicle and Percentage †	Results: Local Vasoconstriction ‡	Results: Blood Sugar, Mg./100 Cc. Before Application	Results: Blood Sugar, Mg./100 Cc. After Application §
1	20	3.0	"Carbitol" (75) 10% HCl ‖ (25)	+	112	108 (130)
1	10	1.5	"Carbitol" (80) 10% HCl (20)	+	108	100 (130)
2	13	1.3	Quinine (5) "Carbitol" (95)	—	124 113	112 (170), 100 (350) 122 (170), 105 (350)
1	10	1.7	"Penetrasol OT"	++	86	172 (180), 330 (300)
1	20	3.6	"Penetrasol OT"	+	111	105 (180), 145 (300)
2	20	2.0	"Carbitol" (45) Octyl alcohol (45) 10% HCl (10)	++	80 104	192 (140) 277 (140), 190 (280)
1	10	2.0	"Carbitol" (45) Octyl alcohol (45) 10% HCl (10)	++	95	360 (140), 320 (280)
1	5	1.0	"Carbitol" (45) Octyl alcohol (45) 10% HCl (10)	++	136	144 (95), 337 (175)
2	2	0.5	"Carbitol" (45) Octyl alcohol (45) 10% HCl (10)	+	112 116	132 (180), 106 (320) 131 (180), 126 (320)
2	1	0.5	"Carbitol" (45) Octyl alcohol (45) 10% HCl (10)	—	117 125	194 (180), 105 (320) 108 (180), 106 (320)
1	5	1.0	"Carbitol" (75) Octyl alcohol (10) 10% HCl (15)	+	128	120 (95), 151 (175)
2	5	1.0	Propylene glycol (45)	++	128	343 (95), 456 (175)
2	1	0.5	"Carbitol" (45) 10% HCl (10)	—	117	109 (180), 105 (320)
1	5	1.3	Benzyl alcohol (73) "Carbitol" (20) 10% HCl (7)	+	106	115 (125), 130 (200)
1	5	2.0	Benzyl alcohol (45) "Carbitol" (45) 10% HCl (10)	+	94	176 (125), 121 (200)
2	5	1.0	Propylene glycol (90) 10% HCl (10)	—	116 112	126 (180), 109 (320) 118 (180), 127 (320)
2	5	0.85	Ethyl alcohol (95) 10% HCl (5)	—	112 132	125 (150), 107 (275) 142 (150), 136 (275)
2	5	1.0	Ethyl alcohol (46) Octyl alcohol (46) 10% HCl (8)	++	104 115	320 (150), 325 (275) 280 (150), 225 (275)

* Dose of epinephrine as base.
† In this column numerals in parentheses indicate percentage of content of each ingredient.
‡ The symbol — indicates no effect, + slight or moderate and ++ intense vasoconstriction.
§ In this column numerals in parentheses indicate minutes after the beginning of application.
‖ Ten per cent HCl means that 10 per cent of hydrochloric acid was added to the mixture to render the dry epinephrine base soluble as epinephrine hydrochloride.

skin. Therefore, we gave preference to the use of the mixture of "carbitol" and octyl alcohol as a vehicle for other drugs.

The percentage of absorption of epinephrine was low, probably below 10 per cent of the dose applied. For instance, 2.0 mg. per kilogram, applied epidermally, did not have any effect on the sugar in the blood of 2 rabbits in which it was tried, while the dose for hyperglycemia given by subcutaneous injection was only one sixth as much, or 0.3 mg. per kilogram.

Epinephrine in "carbitol" and octyl alcohol (1 to 1) was applied epidermally to the clipped abdomens of 2 urethanized (1 Gm. urethane per kilogram given gastrically) rabbits, connected for recording carotid blood pressure on a slow-moving kymograph in the usual manner, using doses of 5 and 10 mg. per kilogram. This resulted in intense local vasoconstriction, but did not affect the blood pressure or the volume of the leg recorded by an oncometer. These negative circulatory results do not eliminate some slight degree of vasoconstriction somewhere in the body, but do exclude outstanding pharmacodynamic changes, considering the large doses of epinephrine applied.

Phenylephrine Hydrochloride.—In doses of 20 and 10 mg. per kilogram, applied to the skin, in solution in "carbitol," phenylephrine hydrochloride ("neo-synephrine hydrochloride") caused local vasoconstriction in 2 normal rabbits, but changes in the sugar in the blood could not be used to estimate percutaneous absorption, since phenylephrine does not affect this function. Phenylephrine hydrochloride, 10 mg. per kilogram, was also ineffective in 1 anesthetized rabbit, and the same dose also had no effect on the blood pressure.

Ephedrine Base.—Epidermal doses of 40 to 20 mg. per kilogram of ephedrine caused local vasoconstriction, but no change in the level of sugar in the blood, in 2 normal rabbits and also in 1 anesthetized rabbit receiving 40 mg. per kilogram.

CHOLINE ESTERS

Of all the drugs which we tried, mecholyl chloride was observed to be the most readily absorbed from the skin. Using doses of 10 mg. per kilogram in octyl alcohol and ethyl alcohol or octyl alcohol and "carbitol" these solutions dropped on the skin, without spreading, produced within two minutes typical symptoms of stimulation of the parasympathetic nervous system, beginning with local vasodilatation, increased peristalsis and defecation, followed by intense salivary secretion and lacrimation with drooling (table 2). These effects persisted for more than two hours. A dose of 1 mg. per kilogram of carbaminoylcholine produced a more pronounced response than a dose of 5 mg. per kilogram of mecholyl chloride applied in the same way and in the same vehicle, which is in accord with their known potency. Acetylcholine bromide in doses of 20 mg. per kilogram produced no symptoms, which might have been due to one of two possible causes:

(1) lack of absorption or (2) enzymatic destruction keeping pace with absorption and thus preventing the systemic actions. The results in table 2 show that the second assumption was correct, since the same dose of 20 mg. per kilogram of acetylcholine bromide applied on the skin, after hypodermic injection of a small dose of physostigmine salicylate (0.1 mg. per kilogram), which in itself was ineffective when tried alone on 2 rabbits, was followed by decided parasympathetic stimulation.

PENICILLIN

A sample of penicillin containing about 1,000 units per milligram was used on 7 rabbits and 3 human volunteers. Samples of blood were

TABLE 2.—*Epidermal Absorption of Choline Esters in Rabbits*

Number of Animals	Drug	Dose, Mg. per Kg.	Concentration, %	Vehicle and Percentage of Content *	Systemic Effects †
1	Mecholyl chloride	20.0	9.0	"Carbitol" (100)	++
1	Mecholyl chloride	20.0	2.0	Water (100)	None
1	Mecholyl chloride	5.0	1.2	"Carbitol" (100)	+
1	Mecholyl chloride	10.0	2.0	Octyl alcohol (80), ethyl alcohol (20)	+++
2	Mecholyl chloride	10.0	2.5	Octyl alcohol (50), "carbitol" (50)	+++
1	Carbaminoylcholine	1.0	0.2	Octyl alcohol (50), "carbitol" (50)	++
1	Acetylcholine	20.0	3.4	"Carbitol" (55), octyl alcohol (35), ethyl alcohol (10)	None
2	Acetylcholine	20.0	5.0	Octyl alcohol (50), "carbitol" (50)	None
2	Acetylcholine and eserine salicylate ‡	20.0 + 0.1	5.0 0.05	Octyl alcohol (50), "carbitol" (50), water	++
2	Eserine salicylate ‡	0.1	0.05	Water	None

* In this column numerals in parentheses indicate percentage of content of the agent.
† Different degrees of parasympathetic stimulation were estimated by the presence or absence of drooling, intensity of reactions and time of appearance of symptoms following application (increasing stimulation with increase in number of plus (+) signs).
‡ Injected hypodermically.

drawn aseptically from the veins and tested against hemolytic streptococci by the method of Wolohan and Cutting.[7] Sodium penicillin was dissolved in 0.1 cc. of water, and then the mixture of equal parts of octyl alcohol and "carbitol" was added to make a concentration of 0.6 to 2.0 per cent and applied on the skin for one hour. The doses of 10,000, 5,000 and 3,000 units per kilogram were absorbed, since two samples of blood, taken thirty and ninety minutes after the application was completed, showed an antibiotic power equivalent to 1.0 unit per cubic centimeter and ¼ unit per cubic centimeter, respectively. Sodium penicillin dissolved in a mixture of equal parts of octyl alcohol, "carbitol"

7. Wolohan, M. B., and Cutting, W. C.: Simple Technique for Estimation of Penicillin in Blood and Other Body Fluids, J. Lab. & Clin. Med. **30**:161, 1945.

and "carbowax 1500" [8] was applied epidermally on 1 rabbit in a dose of 5,000 units per kilogram, with negative results. Negative results were also obtained on the human volunteers with doses of about 700 units per kilogram, dissolved in the same mixture of octyl alcohol, "carbitol" and "carbowax," and in doses of 500 and 1,000 units per kilogram, dissolved in the mixture of octyl alcohol and "carbitol" applied, with rubbing, for ten minutes on the skin of the arm.

MISCELLANEOUS

Insulin.—All the 21 rabbits in which epidermal absorption of insulin [9] was tried gave negative reactions, as indicated by absence of hypoglycemia or convulsions. Insulin was dissolved in "carbitol," in equal parts of octyl alcohol and "carbitol," in "penetrasol OT" and in water. The doses varied from 10 to 200 units per kilogram.

Application of 5 or 6 drops of glycerin before the solution of insulin in water or "carbitol," using doses from 25 to 100 units per kilogram, resulted in no absorption, thus confirming the negative results reported by Bruger and Flexner.[3] In the 2 rabbits in which petroleum ether (5 cc. per kilogram) was applied fifteen minutes before the application of solution of insulin (40 units per kilogram) in water and in "carbitol" (40 units per kilogram), the results were also negative. This refuted the claim of Russell, Busse and Uhl [10] of positive results, but these authors did not state the amount of petroleum ether used and gave no details of its application.

As controls, we injected hypodermically solutions of insulin in "carbitol," in "carbitol" and octyl alcohol and in "penetrasol OT" in 12 rabbits. While insulin in the first two solutions produced the usual effect within two to three hours, it seemed to lose its activity when dissolved in "penetrasol OT" and the effect was delayed, the peak of the hypoglycemia being reached in six to eight hours. This was not due to antagonism of the ingredients in the body, since the subcutaneous injection of 2 cc. per kilogram of "penetrasol OT" did not affect the action of a shock dose of insulin in water, injected also hypodermically.

Di-Hydro-β-Erythroidine.—Single epidermal applications of dihydro-β-erythroidine hydrochloride in doses of 10, 25 and 30 mg. per kilogram were tried on 3 rabbits, using the drug in concentrations of 2 to 5 per cent in the mixture of octyl alcohol and "carbitol" (1 to 1). Following these applications there were no curare-like symptoms which might have indicated that this skeletal muscle paralyzant had been

8. "Carbowax 1500," a semisolid mixture of polyethylene glycols, supplied by the Carbide and Carbon Chemicals Corporation, New York.

9. Supplied by Eli Lilly & Co., Indianapolis.

10. Russell, J. C.; Busse, L. W., and Uhl, A. H.: Studies on the Skin: Cutaneous Absorption of Insulin, J. Am. Pharm. A. **35**:217, 1946.

absorbed. As a control, a dose of 6 mg. per kilogram in the mixture of octyl alcohol and "carbitol" was injected into 1 rabbit, with general muscular paralysis, respiratory stoppage and death within ten minutes.

COMMENT

No attempt was made by us to investigate the full scope of possible agents which might be absorbed epidermally, tests being limited to those which might be used practically with this method and to insulin, for which the claims were contradictory. The three drugs of different type pharmacologically which elicited positive results, without damaging the skin, were epinephrine, choline esters (mecholyl and carbaminoylcholine) and penicillin, all in fairly high doses or concentrations. The percutaneous absorption was determined in most cases by the systemic effects of these drugs. No attempt was made to determine whether the agents, which finally reached the blood stream, had penetrated through the follicular canal or through the stratified epithelium. Whatever the mechanism of penetration, the amount absorbed seemed to be only a small percentage of the dose applied on the skin, making dosage uncertain, if systemic effects were to be desired. On the other hand, cutaneous penetration retains its value for local action in the skin (epinephrine and choline esters and possibly penicillin), and such action might conceivably be desired under certain conditions in which the typical effects of these drugs might be required.

Of all the vehicles used, octyl alcohol mixed with "carbitol" seemed to be the most efficient. However, even with this vehicle, insulin and di-hydro-β-erythroidine failed to penetrate the skin. This tended to corroborate Rothman and Flesch's statement: "Choosing a substance to which the skin is completely impermeable, one will be unable to enforce absorption with any kind of ointment."[11] Whether percutaneous absorption could occur with human skin with the drugs which were observed by us to give positive results when used in octyl alcohol and "carbitol" is not known, but penicillin, the only agent tried, was not demonstrably absorbed under the conditions.

SUMMARY AND CONCLUSIONS

Experiments designed to test percutaneous absorption of selected drugs were made on the clipped skin of rabbits, using as a leading vehicle diethylene glycol monoethyl ether ("carbitol"), which is absorbable and can act as a carrier without damage to the skin, another vehicle being octyl alcohol.

11. Rothman, S., and Flesch, R.: The Physiology of the Skin, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1945, vol. 6, p. 195.

Definite epidermal absorption was demonstrated for the following drugs, according to their typical systemic effects: epinephrine, penicillin and choline esters dissolved in "carbitol" or a mixture of "carbitol" and octyl alcohol. Octyl alcohol mixed with propylene glycol or ethyl alcohol was also effective for promoting the absorption of epinephrine.

Using the same vehicles, insulin and di-hydro-β-erythroidine were not demonstrably absorbed epidermally, thus refuting a previous claim made of positive results for insulin.

Using similar vehicles, large doses of penicillin were not demonstrably absorbed from human skin.

A mixture containing "aerosol OT" damaged the skin and appeared unpromising. For percutaneous absorption vehicles should be relatively noninjurious, but even under most favorable conditions the dosage of drugs tends to be large and absorption irregular for systemic effects. For superficial (intradermal) penetration some of the successful vehicles reported in this paper might be useful for certain drugs, when such action is desired.

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STATUS OF ERYTHEMA ELEVATUM DIUTINUM

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THE DIAGNOSIS and presentation of a case of erythema elevatum diutinum at any dermatologic meeting is usually a signal for prolonged discussion and dispute. The opposing factions are usually divided into those who believe the disease to be a form of granuloma annulare and those who consider it a distinct entity. The purpose of this article is to separate definitely the nebulous delineation of these two dermatoses.

REPORT OF CASES

CASE 1.—J. H., a white man aged 64, when first seen had an eruption of five months' duration. His past history was not significant. He stated that he had not had syphilis or gonorrhea. Furthermore, there was no history of ingestion of drugs which might have been responsible for the lesions.

The eruption appeared on his neck in September 1937 and was not accompanied with subjective sensations. The rest of the lesions appeared within the following two months. They were generalized and consisted of variously sized nodules and plaques, ranging from 0.5 to 4 cm. in diameter (fig. 1 *A* and *B*). There was some tendency toward grouping, especially around the joints. Small aggregate lesions were present about his ears and nose. On both sides of his neck, posteriorly, were clumps of slightly larger lesions. Similar isolated ones were situated on his chest and back. On the extremities there was a tendency toward localization, especially about the wrists and even on the knuckles and dorsum of the proximal articulations of the fingers. The mucous membranes were not involved. All the lesions appeared similar in their general characteristics. They were circular or irregularly oval, arising abruptly from normal skin. The larger ones were plateau-like, while in the others the centers were perceptibly more elevated than the edges. In none was there any evidence of central depression or regression. They varied from dusky reddish brown in the larger to orange-yellow in the smaller ones. Those about the neck might readily have been mistaken for xanthomas. The surface of all was smooth and devoid of crust and scale. The normal cutaneous markings were less distinct than on the surrounding skin. Lanugo hair was absent from the surfaces of the nodules. On palpation they were firm and densely

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infiltrated and did not seem to encroach beyond their visible borders, but could be lifted freely from the subcutaneous tissue.

The patient was well developed, well nourished and apparently in good health. His pupils were normal. His teeth and gums were in poor condition. There was no adenopathy except in the inguinal region, where he had a few tender nodes about the size of a hazelnut. The lungs were normal except for slight wheezing heard at the bases, with some diminution of breath sounds. The cardiac sounds were somewhat diminished, and there was a systolic murmur at the apex. Otherwise his physical condition was essentially normal.

A tuberculin test (Mantoux) gave a negative reaction with 1 to 100,000 dilution but a reaction of 3 plus with 1 to 1,000 dilution. The urine was normal. The Wassermann reaction of the blood was negative. Chemical and cytologic examinations of the blood showed no abnormalities except a slight excess of free cholesterol esters (117 mg. per hundred cubic centimeters). Roentgenograms showed no pathologic changes in the lungs or bones. Several smears of material taken by sternal puncture showed the elements of bone marrow to be normal.

Sections of the nodules were examined histologically. The epidermis showed acanthosis. The underlying corium was granulomatous, showing a profuse infiltration of small and large round cells, many polymorphonuclear leukocytes, fibroblasts, occasional epithelioid cells and numerous eosinophils. In the stroma there was a well defined hyperplasia of spindle cells. A subacute inflammatory process existed about the blood vessels, and there was hyperplasia of the vessels, with toxic necrosis of their walls. This hyperplasia was so intense that some of the lining endothelial cells were gigantic. The fibrils were more or less granular and degenerated and took the eosin stain more strongly than normal. Some of the vessels were more or less completely occluded, although there was no thrombosis. The nuclei of the endothelial cells were pyknotic, and an occasional polymorphonuclear leukocyte was seen within them. (This case was previously reported in the *Archives of Dermatology and Syphilology*.[1])

Case 2.—J. O., a 54 year old white man, was admitted to the dermatologic ward of Bellevue Hospital in March 1945. He presented a nodular eruption involving the ankles, knees and elbows. He stated that in February 1944 he noticed purplish discolorations of the legs. Three months later nodules developed about the ankles (fig. 1 *C*). These increased in size and prevented the patient's wearing shoes. There were no subjective symptoms. Throughout this period the patient noticed a tendency toward profuse bleeding from the cutaneous surface of the entire body following slight trauma. Early in 1945 hoarseness and progressive enlargement of the cervical lymph nodes developed. During a six month stay in the hospital, no new lesions developed. Some of the original nodules spontaneously discharged a sanguineous fluid and subsequently disappeared. Two attacks of erythema multiforme of the bullous type followed the ingestion of barbiturates. The erythrocyte count was always within normal limits, although the leukocytes always numbered above 14,000. The platelet count was normal. The blood cholesterol was 182 mg. and calcium 8 mg. per hundred cubic centimeters. Roentgenograms of the chest disclosed an isolated fibrotic calcification in the apex of the left lung. Roentgenograms revealed that all the bones were normal except for hypertrophic changes in both elbow joints and some calcaneal spurs. Numerous biopsies of various tissues were performed. The first specimen was taken from a lesion on the left ankle in March. The report stated that "the skin was broad

1. Combes, F. C., and Bluefarb, S. M.: Erythema Elevatum Diutinum, Arch. Dermat. & Syph. **42**:441 (Sept.) 1940.

and cornified, without significant change. The papillary layer of the dermis contained dilated lymphatics and a few perivascular lymphocytes and plasma cells. Deeper in the dermis, areas of hyalinized collagen were interspersed with areas of cellular fibrous tissue in which there were many polymorphonuclear leukocytes, a few lymphocytes and plasma cells. Many vascular spaces were present, with some proliferation of the endothelium. Inconstantly, this inflammatory tissue

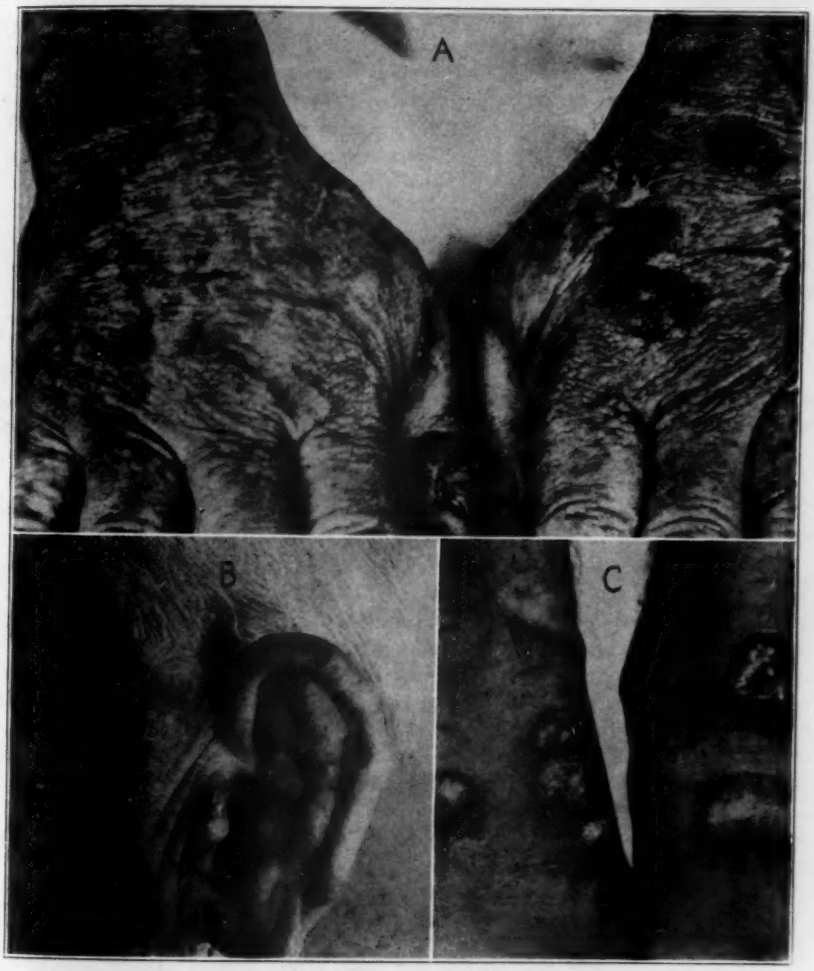

Fig. 1.—Erythema elevatum diutinum *A*, of the hands (case 1), *B*, of the ear (case 1) and *C*, of the feet (case 2).

surrounded sweat glands. A Wilder-Van Gieson stain demonstrated the loss of much of the collagen fibers in the area of atypical tissue. The vascular spaces were numerous."

In April a nodule was excised from the left ankle. This report stated that "the squamous epithelium overlying the nodule was slightly atrophic. The nodule was separated from the epidermis by a thin area of normal corium. The nodular

mass in the corium and subcutaneous tissue was circumscribed but not encapsulated. However, in one area in the deepermost part of the section the lesion was not circumscribed but ran between the collagen fibers. The lesion was composed of irregular masses of connective tissue fibers arranged in whorls. The nuclei of these cells were usually elongated, but in some areas were irregularly round. They showed mild to moderate pleomorphism and were generally vesicular. There was a moderate focal infiltration of polymorphonuclear leukocytes and eosinophils. A Masson trichrome stain demonstrated a moderate number of capillaries within the tumor mass and the presence of much collagen. The Wilder-Van Gieson stain demonstrated the presence of enormous numbers of reticulum fibers." The diagnosis of Kaposi's sarcoma was advanced on the basis of this section.

A lymph node was removed from the axilla at the same time. The histologic examination revealed that "the capsule of the lymph node was intact and did not show any abnormal cells. The lymphoid tissue and reticulum cells were hyperplastic, so that in some areas the sinus architecture was obliterated. In a few small areas there was fibrosis of the node, and in these areas some large mononuclear cells contained brown pigment." The tissue was reported as chronic lymphadenitis.

In May a lesion of the "erythema multiforme" type was removed from the back of the neck, on which the following report was submitted.

"The epidermis exhibited mild acanthosis. The dermal capillaries were surrounded by thick mantles of lymphocytes and large mononuclear cells. There were a moderate number of polymorphonuclear leukocytes. Occasional mononuclear cells in the superficial dermis contained golden brown pigment granules.

"Brown and acid-fast stains failed to demonstrate organisms in the section. A Weigert-Van Gieson stain showed loss of elastic fibers in the areas of cellular infiltration." The histologic interpretation was erythema multiforme.

In July a mass was removed from the right nasopharyngeal region. The histologic examination showed the section to consist of "small fragments of tissue incompletely covered on one side by stratified squamous epithelium. The nuclei of these epithelial cells were for the most part round and vesicular, and nearly all contained one or two prominent nucleoli. In some of these, mitotic figures could be seen. While in most areas the epithelium was sharply demarcated from the underlying tissue, in some regions this delineation was lost and the epithelial cells merged with those of the subepithelial connective tissue. In the underlying connective tissue there was a moderate infiltrate of lymphocytes and plasma cells and a few polymorphonuclear leukocytes. The rather dense connective tissue was moderately vascular." A diagnosis of chronic inflammatory changes was made after study on this section.

In July a lesion was removed from the periarticular region of the ankle. The report was as follows:

"The epidermis was normal in thickness and rete peg formation. There were focal areas of lymphocytic infiltration in the corium, some of which were in relation to small blood vessels, but others of which did not exhibit this relationship. In some areas a number of polymorphonuclear leukocytes were seen interspersed throughout the lymphocytic aggregations, chiefly in their central portions. In the deepest portion of the corium and in the subcutaneous tisse there was a nodular mass of tissue which was fairly well circumscribed. This mass was made up of proliferating fibroblasts and collagen fibers, which in some areas showed a parallel arrangement. The main mass in most areas was broken up into smaller masses of the proliferating fibroblasts and collagen fibers by dense bands of adult fibroblasts and collagen fibers. In the smaller masses there was a mild to decided

infiltration of polymorphonuclear leukocytes and lymphocytes. In the smaller masses, in which the polymorphonuclear leukocytic infiltration was decided, the central portion of the mass was undergoing necrosis. Occasionally the cells arranged around the central area of early necrosis had a suggestive epithelioid appearance. A few of the cells within these nodular masses appeared to be vacuolated. A rare mononucleated giant cell was present (fig. 2).

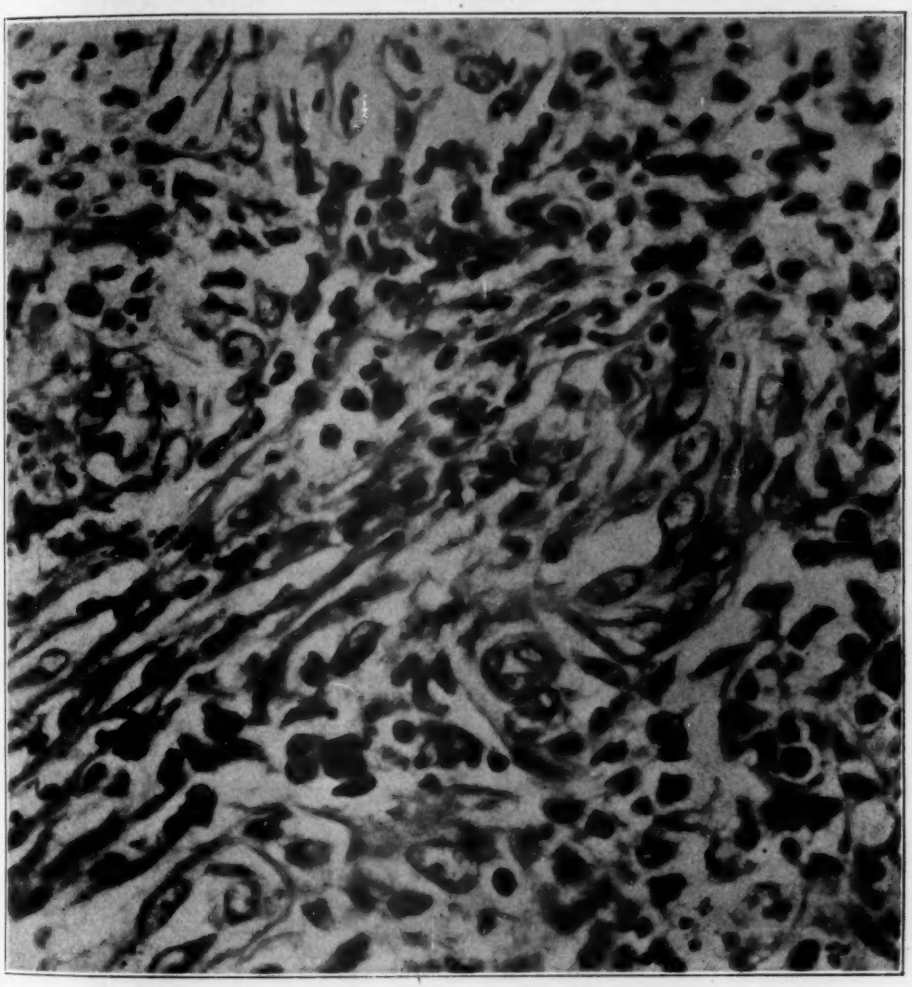

Fig. 2.—Histologic section of a nodule on the ankle (case 2). This section shows several groups of polymorphonuclear leukocytes in close proximity to small blood vessels, an observation usually considered typical of erythema elevatum diutinum.

Brown and acid-fast stains failed to demonstrate any organisms.

A Wilder-Van Gieson stain "demonstrated a moderate number of reticulum fibers in the nodular mass except in the central areas of early necrosis and polymorphonuclear leukocytic infiltration."

In connection with this section, Dr. W. C. Van Glahn reviewed the nodular sections which had been removed in March and April. He stated that "the lesion shown in each of these three sections appeared to be the same, though in different stages of development." The diagnosis of Kaposi's disease appeared to be untenable. He suggested the diagnosis of a "granulomatous lesion of undetermined type." Dr. Fred Weidman examined the sections and stated that he was "unable to see a resemblance to Kaposi's sarcoma. The processes were neither hemorrhagic nor pigmentary, and the blood vessels were thick walled. The polymorphonuclear leukocytes certainly did make one think strongly of erythema elevatum diutinum. The other possible disease was juxta-articular nodules, but in the ones seen in previous cases there had not been such a consistent aggregation of polymorphonuclear leukocytes adjacent to the blood vessels. The plasma cells which were present gave more weight to the idea of juxta-articular nodules, but since the lesions were not reported as being particularly in relation to the joints the diagnosis of erythema elevatum diutinum was favored.

COMMENT

Historically, the disease was first described by Bury [2] in 1889. In this small group of cases Bury proceeded to describe a disease picture of close similarity to that of granuloma annulare. However, some of the features which he described are most commonly encountered in the full-blown picture of erythema elevatum diutinum. For this reason, the name of Bury was applied to those cases of granuloma annulare which showed a few of the characteristics of both diseases. In other words, the so-called Bury type is merely a variant of granuloma annulare.

Hutchinson [3] had also described "two remarkable cases of symmetrical purple congestion of the skin in patches with induration." These 2 cases were probably the first distinct instances of erythema elevatum diutinum, and for this reason the frank cases of this disease are often referred to as of the "Hutchinson type." Much of the confusion relevant to this entity seems to have arisen at a later date as a result of the article written by Radcliffe-Crocker and Williams.[4] They included in their description of erythema elevatum diutinum (the first to describe it under this name) the case first reported by Bury and more closely resembling granuloma annulare. If they had separated the Bury variant of granuloma annulare from the Hutchinson type of erythema elevatum diutinum, they would have prevented much of the later confusion pertinent to this disease. Accordingly, in 1908, Little [5]

2. Bury, J. S.: A Case of Erythema with Remarkable Nodular Thickening and Induration of Skin, Associated with Intermittent Albuminuria, Illust. M. News **3**:145, 1889.

3. Hutchinson, J.: On Two Remarkable Cases of Symmetrical Purple Congestion of the Skin in Patches with Induration, in Lectures on Clinical Surgery (On Certain Rare Diseases of the Skin), London, J. & A. Churchill, 1878, vol. 1, pt. 1; Brit J. Dermat. **1**:10, 1888-1889; Arch. Surg. **1**:372, 1890-1891.

4. Crocker, H. R., and Williams, C.: Erythema Elevatum Diutinum, Brit. J. Dermat. **6**:1 (Jan.) 1894.

5. Little, E. G. G.: Granuloma Annulare, Brit. J. Dermat. **20**:213 (July) 1908.

made a survey of the subject and unfortunately concluded that erythema elevatum diutinum was a subvariety of granuloma annulare; but the cases he collected from the literature were limited to the so-called Bury type. In later years, however, Little stated that the disease differed from granuloma annulare and that this difference was primarily in the absence of discrete nodules. In 1929 Weidman and Besancon,[6] in presenting 2 cases, made a comprehensive bacteriologic and histologic study of the disease. From a lesion in 1 of the patients they isolated Streptococcus ignavus, which they submitted as a possible causative agent. They also stressed the rheumatic background in a majority of

Summary of Differential Diagnosis Between Erythema Elevatum Diutinum and Granuloma Annulare

	Erythema Elevatum Diutinum	Granuloma Annulare
Age (years)	40 to 60	5 to 30 (especially children)
Distribution	Bilateral and roughly symmetric	Unilateral usually
Duration of lesions	Persistent	Fade and reappear
Histologic examination	Preeminently an acute tissue process, with characteristic polymorphonuclear leukocytes and eosinophils but no necrosis	Process varies from subacute to chronic, with fibroblastic proliferation as the predominant reactive expression and extensive necrosis
Individual nodules	Not discrete	Typical discrete nodules
Lesions	Flat, raised and red, with no central clearing	Colorless or pink ring of nodules, with center of normal skin (or slight atrophy)
Location	Hands, feet and less commonly on wrists, ankles, neck, knees and buttocks, in descending frequency	Hands, feet and less commonly on wrists, ankles, neck, knees and buttocks, in descending frequency
Response to treatment	Radioresistant	Radiosensitive
Scar formation	If ulcerated, lesions heal leaving deeply pigmented scars	None, heal leaving no trace
Seasonal variation	None	Most frequent during summer
Sex	Men (middle aged and elderly)	Women (and children)
Ulceration	Possible	Never break down or ulcerate

the reported cases. On the basis of histologic examinations, they stated the belief that erythema elevatum diutinum was the cutaneous expression of bacteremia, distinct from granuloma annulare. After a carefully made study they concluded:

The major pathologic changes may be gathered and interpreted under two headings: (1) an acanthosis in the epiderm and (2) an acute toxic periarteritis and peritelangiitis in the corium. The acanthosis was not of the most extreme grade possible, being rated as grade II in this laboratory. The excessive thickening of the stratum corneum must be due in greatest part to rubbing on such exposed positions as are concerned in this dermatosis; but, in view of the intensity of the toxic changes observed deeper, we believe that these at least add to the

6. Weidman, F. D., and Besancon, J. H.: Erythema Elevatum Diutinum, Arch. Dermat. & Syph. **20**: 593 (Nov.) 1929.

mechanical factors, if there are such in the case, although no infiltration of leukocytes could be seen actually within the epiderm.

As to the acute exudative feature in the corium, this is fully as acute a process as that of erysipelas, but showed damage to the blood vessel walls . . . in a much more definite way than in erysipelas. The extremeness of the toxic hyaline change seen in the older lesions is, in our experience, pathognomonic, but we must at once emphasize that reliance must not be placed on this alone for the diagnosis . . . .

As far as we know, this is the only dermatosis (of the skin proper) in which masses of polymorphonuclears dominate the picture, apart from such severe acute fulminating conditions as erysipelas and cellulitis and perhaps erythema nodosum.

A study of the disease brings out definite characteristics distinct from those of granuloma annulare. These are summarized in the accompanying table.

SUMMARY

A review of pertinent literature and a study of 2 cases of erythema elevatum diutinum prove that this disease is a specific nosologic entity. The so-called Bury type is merely a variant of granuloma annulare. The Hutchinson type is synonymous with the disease itself and should be labeled erythema elevatum diutinum. The features which distinguish this disease from granuloma annulare are summarized in the appended table.

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CHEESE MITE DERMATITIS OCCURRING IN THE UNITED STATES

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THIS paper is written because we feel that the importance of cheese mite dermatitis has been long overlooked and the disease has been long unrecognized by American dermatologists. As far as can be ascertained, this is the first reported case of cheese mite dermatitis of American origin and of mite dermatitis from American-made cheeses.

REPORT OF A CASE

B. B., aged 32 and a white sturdy light complexioned man, was seen in October 1945, complaining of an itching eruption of the arms and area about the waist, of two weeks' duration. He was a worker in a wholesale food distributing plant. The day prior to the onset of his rash he lifted and carried large black-coated "wheels" of Romano cheese, holding the cheese in his arms against his abdomen and chest. He had worn a loosely knit sweater and no shirt or underclothing and had perspired considerably.

Physical examination revealed an extensive eruption involving the entire anterior aspect of the trunk (most evident on the abdomen) and the inner aspects of the arms and forearms. The lesions were discrete erythematous papules of varying sizes, each papule having a small central vesicle. Lesions removed with a razor blade showed no mites or scabies organisms in microscopic examination.

He was treated with a 25 per cent benzyl benzoate emulsion and roentgen rays (75 r). In one week, only a few crusted excoriations remained.

Scrapings were made at the food processing plant from the cheeses that the patient had been in contact with at the onset of his dermatosis. Many mites of the Tyroglyphus longior[1] variety were seen. The cheese debris was partially removed by washing repeatedly with ether, and the mites could be plainly seen under the microscope. For permanent mounts some were first cleared with 40 per cent potassium hydroxide and some fixed only with Berlocq's solution. Eggs, young mites and adults were easily seen in all slides.

Read at the annual meeting of the Dermatological Section of the California Medical Association, Los Angeles, May 10, 1946.

1. Banks, N.: A Revision of the Tyroglyphidae of the United States, Technical Series 13, United States Department of Agriculture, Bureau of Entomology, 1906, pp. 1-34; The Acarina or Mites, Report 108, United States Department of Agriculture, Office of the Secretary, 1915, pp. 1-153.

The cheeses in which mites were observed were the Romano cheese, in large black-coated "wheels," made in Ojai, Calif., and small packages of Cheddar cheese, made in Denver. On the Cheddar cheese, the mites were seen most plentifully in a brownish red dust over the surface of the cheese.

Fig. 1.—Cheese mites, adult and young, and egg (magnification × 154).

The patient stated that his co-worker, an older white man who had been carrying the large cheeses in a similar manner, had a similar rash of about the same distribution, but less extensive. His dermatosis subsided in a couple of weeks with the application of calamine lotion. The onset in both men was almost simultaneous, i. e., about twenty-four hours after contact with the large cheeses.

Fig. 2.—Cheese mite (adult) (magnification × 208).

DESCRIPTION OF CHEESE MITE

Thomas [2] had Mr. E. Browning of the Department of Zoology, British Museum of Natural History, describe the cheese mite minutely, and his modified description follows.

The mites in the cheese dust agree in detail with the mite described by Hirst [3] as Tyroglyphus longior var. castellanii, which causes itch in handlers of copra. The mites are pale and soft bodied, with two large chelate mandibles and four pairs of legs of moderate length, each ending in a single claw. The body is polished and without markings. The cephalothoracic portion is almost conical, its base being narrower than its abdomen, from which it is divided by a deep sulcus. The abdomen is truncated anteriorly, has almost parallel sides and is rounded posteriorly. The body hairs are long. The penis of the male is placed between the fourth pair of legs and is protected by chitinous sclerites forming a blunt triangle. The anal opening of the male is a longitudinal slit in the ventral surface, extending from a little behind the penis to more than halfway toward the hind margin; close to its posterior end are a pair of suckers. There are also two suckers on the upper surface of the fourth tarsus near the middle in the male mite. The vulva of the female mite is between the third and fourth pair of legs; it is almost conical, turning upward at its posterior end. The anal opening of the female mite is farther back than that of the male and is without suckers. Hirst [3] based his variety of Tyroglyphus on the absence of a pair of short hairs posteriorly of the anal suckers on the male mite.

CLINICAL IMPORTANCE OF TYROGLYPHID MITES

Tyroglyphid mites are worldwide in distribution. They have been reported in cheese,[4] flour, sugar, hams, dried meats, hair in furniture, mattresses, pillows, grain in mills, cereal foods, many drugs, wine, dried fruits, jams, jellies, seeds of many kinds, bulbs, roots of plants, mushrooms, feathers, hay, refuse in nests, scale insects, pinned insects of entomologic collections and even human corpses. They have been reported even in urine, feces and the vulva and as causing gastric and intestinal irritation.

The following tyroglyphid mites have been reported as having given rise to cutaneous trouble: Aleurobius farinae (Linn) (causes severe itching in persons handling wheat), Carpoglyphus passularum (Hering)

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2. Thomas, E. W.: Dermatitis Due to Tyroglyphus Longior, Gerv. Var. Castellani, Hirst, in Cheese Dust, Brit. J. Dermat. **54**:313-319, 1942.

3. Hirst, S.: Report on the Mite Causing the Copra Itch, Proc. Roy. Soc. Med. (Dermat. Sect.) **6**:29-31, 1912-1913.

4. Solomon, M. E.: Tyroglyphid Mites in Stored Products, Department of Scientific and Industrial Research, London, His Majesty's Stationery Office, 1943; supp., 1944, Thomas.[2]

(causes occupational dermatosis in persons handling spoiled dates, prunes and plums),[5] Glyciphagus domesticus (de Geer) (grocer's itch), Rhizoglyphus parasiticus (Dalgetty) (in cutaneous eruptions in workers on a tea plantation in India) and Tyroglyphus longior var. castellanii (Hirst) (causes copra itch and cheese mite dermatitis).[6]

HABITAT OF CHEESE MITES

According to Patton [7] and Thomas [2] the cheeses mainly attacked are those that have been kept a considerable time in storage. In Britain, Stilton and Cheddar are most commonly invaded. The mites, which are said to be present in many cheese dairies, can be observed in dust and scrapings from the shelves. They apparently crawl onto the cheese, select a minute hole or crevice and eat their way into the cheese. Eggs are laid, and a flourishing colony is soon established. On the surface of the cheese a coating of fine powder forms, which may be ¼ inch (about 0.64 cm.) thick, composed of layer on layer of dead bodies of mites, moulted skins, feces, minute particles of uneaten cheese and the living mites themselves. Mite-infected cheese can be recognized by this fine brown powder and by the numerous small holes and cavities. Apparently mites are sometimes artifically cultured in certain cheeses, notably Altenburger, in order to give them a slightly sour flavor. Patton stated that probably the most frequent mode of accidental infestation is by insects, especially certain flies, and to avoid this he advised keeping cheeses in a cool light well screened place with scrupulously clean shelves. A paraffin coat, if kept unbroken, will prevent cheeses being attacked, and all infested cheese should be removed at once.

These mites are not, of course, related in any way to the maggots sometimes seen in cheese. These are the larvae of a fly, Piophila casei, which lays its eggs on the cheese and the maggots or larvae of which bore their way in. When disturbed they have the peculiar habit of springing or jumping ("cheese skippers"). They are much larger than the mites. Eggs are about 1 mm. long and full-grown larvae 7 to 9 mm.

HISTORICAL SKETCH

Castellani [8] in 1912 discovered that copra itch was caused by a mite, and Hirst [3] with Castellani described the copra mite and classified it entomologically as a new variety of the species T. longior, family Tyroglyphidae of the order Acarina, attaching to it the name castellanii.

5. O'Donovan, W. J.: Dermatitis Due to Carpoglyphus Passularum, Brit. J. Dermat. **32**:297, 1920.

6. Eales, N. B.: Life History and Economy of the Cheese Mites, Ann. Biol. **4**:29, 1917.

7. Patton, W. S., and Evans, A. M.: Insects, Ticks, Mites and Venomous Animals of Medical and Veterinary Importance, Croydon, H. R. Grubb, Ltd., 1931, pt. 2, p. 684.

8. Castellani, A.: Copra-Itch (Due to a Sarcoptes), Brit. M. J. **2**:1208, 1912.

Whitfield [9] in 1915 described a patient with copra itch and demonstrated the mite he had obtained from cavities in pieces of copra. Macleod [10] in the same year reported a case of copra itch in a dock laborer who had been shoveling a cargo of broken copra from the hold of a ship. The mite was not seen. Schwartz and Tulipan [11] said that the mites seen in cheese and flour seemed nonpathogenic, but they mentioned, as did White,[12] that tyroglyphid mites may be responsible for "grocers' itch" and that in workers in sugar refineries and chocolate and candy factories dermatoses may develop from them.

Cleveland [13] in 1940 described a case of cheese mite dermatitis occurring in Canada. His patient had been employed for five days in a wholesale grocers' warehouse, unpacking large Canadian cheeses from drums and scraping off the powdery deposit on their flat surfaces. He presented slight edema of the cheeks and lower eyelids and a symmetric distribution of an erythematopapular rash, chiefly on the volar surfaces of the forearms and of the arms a little above the elbows, the neck and the face. The cheeses were lifted and carried on the bare arms. Scrapings of the cheese were seen to be swarming with the mites, which were about the same length as scabies mites but little more than half their breadth. The eggs, also, resembled but were slightly smaller than those of the scabies mite. Since parasites were not seen in the skin after repeated examination of the cheese handler, Cleveland expressed the belief that the mites behave as the body louse does, remaining on the skin only while feeding and that they are not parasitic. He therefore expressed the opinion, as Castellani [8] did, that antipruritic and antiseptic rather than parasiticidal treatment was indicated. His patient, however, was treated with sulfur ointment. For prophylaxis, he advised daily covering of the exposed parts with white petrolatum before work and washing thoroughly with ordinary soap after work.

Thomas [2] in 1942 reported 3 cases of cheese mite dermatitis occurring in England. His patients were unloading cheeses and were showered with the fine brown powdery dust which covered the surface of the cheeses. About twenty-four hours later his first patient noticed that his face and forearms began to prickle and itch and that his eyelids swelled. On examination the patient presented diffuse erythematous

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9. Whitfield, A.: Acarus from a Case of Copra Itch, Proc. Roy. Soc. Med. (Dermat. Sect.) **8**:116, 1914-1915.

10. Macleod, J. M. H.: Note on a Case of Acute Dermatitis Due to Copra Dust. Brit. J. Dermat. **27**:118, 1915.

11. Schwartz, L., and Tulipan, L.: Occupational Diseases of the Skin, London, Henry Kimpton, 1939, p. 462.

12. White, P. R.: The Dermatogeses, London, H. K. Lewis & Co., Ltd., 1934, p. 415.

13. Cleveland, D. E. H.: Mite Dermatitis, Arch. Dermat. & Syph. **41**:831-834 (May) 1940.

dermatitis of the forehead, face, ears and front and sides of the neck and edema of the eyelids. The lower portions of the flexor aspects of both forearms were similarly involved, but also showed a number of urticarial lesions. The second patient presented milder dermatitis of similar type and distribution. In the third patient an eruption developed some thirty-six hours after he had started the work, and he presented an acute diffuse erythematopapular eruption of typical contact dermatitis on the forehead, face and neck, with edema of the eyelids and slight conjunctivitis. All 3 patients brought specimens of cheese dust, which was observed to be teeming with mites. Treatment with calamine liniment brought rapid subsidence of the dermatitis.

Nixon [14] in 1944 reported cheese mites, identified as T. longior, causing dermatitis in English stevedores who had unloaded a cargo of cheese. The mites were observed only in a gray feathery mold on muslin covering the cheese. He, incidentally, stated that in 1915 he observed, on investigating complaints made by dock laborers of an irritating eruption which developed after they had unloaded a cargo of cotton seed, that the cotton seed was full of a mite known to give rise to such an eruption, namely, Pediculoides ventricosus. In the discussion of Nixon's paper, Thomas mentioned numerous outbreaks of cheese itch, linseed itch and copra itch between 1942 and 1944 in the Port of Glasgow, Scotland. In the same paper, Sybil Horner and Louis Forman also mentioned cases of cheese mite dermatitis in England.

MODE OF IRRITANT ACTION

From the appearance of the dermatitis in our patient, discrete erythematous papules with a small central vesicle, it was first assumed that these were the result of bites of the cheese mites. Some interesting speculation on the exact mode of irritant action of the cheese mite, however, has been made recently in the literature.

Peck, Wright and Gant [15] in 1943 experimentally observed that repeated exposures to the body louse resulted in the development of a dermal hypersensitivity in the majority of those exposed and that the feces of the louse plays an important role in this induced reaction. As in cheese mite dermatitis, there is usually a lag of over twenty-four hours between exposure and the appearance of symptoms. The point comes up that this is more like contact dermatitis rather than like a bite, from which one would expect irritation shortly after exposure. In many of the patients with cheese and copra dermatitis reported there has been diffuse erythematous dermatitis rather than lesions suggesting individual bites.

14. Nixon, J. A.: Cheese Mite and "Itchy Cargoes" in Reference to Workmen's Compensation, Brit. J. Dermat. **56**:235-241, 1944.

15. Peck, S. M.; Wright, W. H., and Gant, J. Q.: Cutaneous Reactions Due to the Body Louse (Pediculus Humanus), J. A. M. A. **123**:821-825 (Nov. 27) 1943.

Sybil Horner [16] brought up the point that in copra dermatitis perhaps the essential oil in copra dust plays a part or perhaps inhalation of the copra dust has some part in the production of the urticarial type of eruption occasionally seen. Horner also discussed the fact that in harvest mite dermatitis the adults are said not actually to bite the human host but to deposit the larvae on the skin, while the mites set up a severe cutaneous irritation with their salivary secretion.

G. B. Dowling [16] suggested that there may be some rather powerful chemical irritant in the tyroglyphid masses and that it would be interesting to know whether masses of dead mites would have the same effect. The Port Medical Officer at Glasgow said, according to Dowling, that in the worst outbreak of cheese mite dermatitis the mites were dead.

Thomas [2] performed patch tests in 25 subjects with cheese dust which contained numbers of undisintegrated bodies of mites, which was more than two and a half years old and which was inactive on microscopic examination. The areas were examined in forty-eight or seventy-two hours. The reactions in 7 subjects were strongly positive (raised erythema with papules and vesicles); in 3 they were positive (raised erythema only), and in 15 they were negative.

TREATMENT AND PROPHYLAXIS

From a review of the literature it seems that the dermatitis may be best treated with any antipruritic and antiseptic lotion or ointment, as the rash clears rather quickly when further exposure is discontinued. As the mites do not live on the skin, no parasiticidal agent is necessary. Contaminated clothing should be thoroughly cleaned to prevent continued contact.

Prophylactically, prevention of intimate contact with the skin by wearing gloves and closely knit covering clothes or application of a surface protective agent, such as petrolatum, seems all that is necessary, provided that a thorough washing of all possible exposed contact areas is done with soap after the day's work is finished.

SUMMARY

A case of cheese mite dermatitis is presented, which is believed to be the first case reported occurring in the United States and from American cheeses.

Included is a description of the cheese mite, comments on the clinical importance of tyroglyphid mites and the habitat of mites, historical review of reported cases, treatment and prophylaxis and presentation of speculations on the mode of irritant action of the cheese mite.

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16. In discussion on Nixon.[14]

VOGT-KOYANAGI SYNDROME

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THE RARE disease, Vogt-Koyanagi syndrome, has not been previously described, to our knowledge, in the dermatologic literature. Inasmuch as the few reported cases have appeared only in the annals of ophthalmology, the present case is deemed worthy of presentation as an example of this syndrome, the chief manifestations of which are uveitis, canities, alopecia, vitiligo and dysacousia (certain sounds produce discomfort)

REPORT OF A CASE

History.—I. S., a white woman aged 42, was first observed on June 12, 1943, with an erythematous scaling eruption involving the eyelids and surrounding skin. Subsequent examinations and observations proved the eruption to be contact dermatitis, which subsided on the removal of the offending agent, i. e., nail polish. Within the course of one year, the eruption underwent several remissions and exacerbations, until the patient was finally convinced, to her own satisfaction, that she was unable to tolerate nail polish. At the end of this period, she complained of difficulty in reading small print and was, accordingly, referred to one of us (J. L.) for ophthalmologic examination.

Ophthalmologic Examination.—The results of the ophthalmologic examination in May 1944 were entirely negative except for the observation of a few cells in the aqueous of each eye, more in the left. The patient read the smallest print by the addition of —1.25 D. sphere to each lens. However, the few cells in each anterior chamber, as seen with the slit lamp, could not be explained, inasmuch as both eyes were white; there was no photophobia, and there were no ocular complaints other than the difficulty with near vision. The intraocular pressure in each eye was 18 mm. of mercury (Schiøtz).

The patient was given 1 per cent paredrine hydrobromide ophthalmic [1] three times daily, so that her accommodation would not be interfered with, thus allowing her to continue with her work as a secretary. When she was seen again, four days later, the cells in the aqueous had not increased and the vision was the same, but the fundi now showed an unusual picture. Both optic disks were hyperemic; the margins were fuzzy, and the lower half of each retina was yellowish. On

1. Paredrine hydrobromide ophthalmic is a 1 per cent solution of *p*-hydroxy-*a*-methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved with merthiolate, 1 to 50,000.

the following day the patient noticed "a big black spot" in front of each eye, and it was observed that there was a central scotoma for colors in the right eye and an absolute central scotoma for colors and form in the left eye. The fundus picture was changing, and edema was present at both maculas.

An examination was carried out for possible foci of infection in the vicinity, and the antrums were observed to be moderately involved. The sinuses were opened and drained.

On June 5, five days after the sinuses were opened, the visual loss and retinal edema had progressed. Now, for the first time, fine deposits were seen on the posterior elastic lamina, with an increase of cellular contents in the aqueous of each eye. The margins of both disks were obscured, and the retinas were edematous and yellow. They bulged forward, so that one had the impression of looking into a funnel with the optic disk at the narrow end.

The patient was admitted with a tentative diagnosis of Vogt-Koyanagi syndrome to the Eye Service of the Mount Sinai Hospital, where thorough laboratory investigations could be carried out.

Course.—Several days after admission a symmetric bullous detachment of the inferior aspect of both retinas was noted, but no tear was observed. A lumbar puncture after admission showed 725 lymphocytes, with a total protein of 74 mg. per hundred cubic centimeters, and a culture was negative. At no time did the patient show meningeal or any other neurologic signs. During her stay the spinal fluid gradually cleared of cells.

Examination of the scalp showed several scattered dime-sized to quarter-sized irregularly oval areas of alopecia. There were no exclamation point hairs present at the margin, although the appearance was typical of that of alopecia areata, and the involved areas of skin were entirely normal. The dermatitis of the eyelids had disappeared. The patient also began to show signs of some loss of hearing.

The eyes showed little change except for increased haziness of the vitreous and decreased vision. However, for the last week of her stay there seemed to be some improvement, despite a few days of exacerbation of symptoms. The patient had moderate ocular pain, malaise and some fever. Both spinal fluid and aqueous were taken for virus studies and inoculation of animals, the results of which are as follows:

The procedure used was the injection of a mixture of 0.1 cc. of aqueous with 0.5 cc. of spinal fluid into the anterior chamber of a rabbit and 2 guinea pigs, the bathing of the scarified corneas of 2 mice (white) with the same mixture and the injection of aqueous alone into the anterior chamber of 1 rabbit. All were done bilaterally. The amounts injected were 0.05 cc. into the rabbits (each eye) and 0.01 cc. into the guinea pigs.

All animals were autopsied. One rabbit died within four days of a febrile illness. The others died within the following month (or were killed), without any suggestive ocular or meningitic symptoms or autoptic observations with the exception of symptoms in one eye of 1 mouse. The apex of the cornea became cloudy centrally and remained so for three weeks, because of deep keratitis with exudate in moderate amount in the anterior chamber and some iritis. The exudate consisted of fibrin, lymphocytes and a goodly number of polymorphonuclear lymphocytes. There were, likewise, mixed cells in the adjacent cornea, which was slightly edematous. Nothing suggestive of inclusion bodies was observed even in the Giemsa-stained slides. The epithelium of the cornea seemed to have regrown in this region. The animal was otherwise asymptomatic. The impression was that the animal's keratitis was based on secondary infection and that results for the

entire series were negative, including examination of specimens of aqueous and spinal fluid for virus studies. Cultures of the spinal fluid were negative; the serum showed no agglutinins against Brucella abortus and Brucella melitensis. The electron microscopic study of the aqueous and spinal fluid showed no virus-like bodies.

Treatment.—During the patient's stay in Mount Sinai Hospital the treatment was as follows: A full course of penicillin, 700,000 units over five days, was given. Four courses of fever (typhoid) therapy were administered intravenously, temperatures above 104 F. being maintained for at least four hours after each injection. Local treatment for the iritis and attention to foci of infection, including the sinuses, were continued. However, there seemed to be no definite response to any of these, and it was felt that the patient would have to sustain the natural course of the disease.

On August 18 the patient showed moderate poliosis of the lashes of each upper lid, and the eyebrows were entirely gone, with alopecia and grayness of the few hairs left on her scalp. There was no vitiligo, and none was seen at any time even with filtered ultraviolet rays. On September 8 a modified Lagrange operation with complete iridectomy was performed on the left eye at Manhattan Eye, Ear and Throat Hospital. On November 9 a modified Lagrange operation with complete iridectomy was performed on the right eye, and there was no postoperative reaction at all. The iridic tissue that was excised was similar to that obtained from the left eye. Because of the contact dermatitis from atropine, scopolamine hydrobromide was ordered for both eyes. The patient gradually became allergic to scopolamine hydrobromide, and 10 per cent "neo-synephrine hydrochloride" (phenylephrine hydrochloride) was given once daily.

During this period the patient had been treated for the alopecia with mild rubefacients, phenol applications and ultraviolet radiation. By January 1945 the areas of previous alopecia were covered with a downy white fuzz, which gradually lengthened to several inches. The eyebrows were slow in growing back. In June examination showed that the hair on the scalp was practically normal in appearance. The gray and white patches were almost black, with streaks of gray, and the eyelashes were their normal dark shade.

COMMENT

There have been several reports of uveitis [2] associated with poliosis, dysacousia, alopecia and vitiligo. In this report there are at least two contributions of interest, one clinical and the other pathologic. The clinical observation is unusual in that the patient was seen so early in the course of the disease that the only abnormal observation was a few cells in the aqueous. The pathologic contribution consists of a study of the iridic tissue of each eye of the patient. A possible third point of interest is the observations of the spinal fluid and the studies made on the aqueous of one of the diseased eyes. This has been done before, but so infrequently that only four other investigators have reported examinations of spinal fluid and only two others examinations of the aqueous.

2. (*a*) Rones, B.: Uveitis with Dysacousia, Alopecia and Poliosis, Arch. Ophth. **7**:847 (June) 1932. (*b*) Davies, W. W.: Uveitis with Associated Alopecia, Poliosis, Vitiligo and Deafness, ibid. **14**:239 (Aug.) 1935.

Vogt [3] was the first to call attention to the syndrome, but Koyanagi [4] was preceded by several others. It is true that Koyanagi added dysacousia and alopecia, but the disease had been recognized and treated for some time before Koyanagi's paper appeared. One should not ignore the work of Gilbert,[5] Elschnig, Erdmann [6] and Komoto.[7] So-called Harada's disease is the same, without involvement of the anterior uvea. And one should remember that not in all cases are there all the features of the syndrome; one or more may be missing, but still the diagnosis is made.

In 1910, Gilbert, in discussing his case, suggested that a herpetic lesion might be the causative agent. Investigators today are still looking for a virus as the possible causative factor. In 1911, both Komoto and Erdmann supported Gilbert's theory when they discussed their own cases. In 1929, when Koyanagi presented his paper, he could add nothing to the causation or the pathology, but he did add two additional signs to the syndrome, namely, alopecia and dysacousia, which may occur in some of the patients. In 1930, Takahashi [8] carried out some experiments with animals and came to the conclusion that a virus was responsible, a concept possibly similar to that entertained for sympathetic ophthalmia or herpetic lesions, again no further advanced than Gilbert's concept in 1910. In 1939 Magitot and Dubois-Poulsen [9] had a case in which there were cells in the spinal fluid, and they expressed the opinion that a virus was the causative agent. In 4 of Takahashi's 6 cases the reactions of the spinal fluid were positive; that is, they contained cells. Malbran and Muhlmann [10] expressed the thought that Harada's disease in their case was due to a "neurotropic virus" similar

3. Vogt, A.: Frühzeitiges Ergrauen der Zilien und Bemerkungen über den sogenannten plötzlichen Eintritt dieser Veränderung, Klin. Monatsbl. f. Augenh. **44**:228, 1906.

4. Koyanagi, Y.: Dysakusis, Alopecia und Poliosis bei schwerer Uveitis nicht traumatischen Ursprungs, Klin. Monatsbl. f. Augenh. **82**:194, 1929.

5. Gilbert, W.: Vitiligo und Auge, ein Beitrag zur Kenntnis der herpetischen Augenerkrankungen, Klin. Monatsbl. f. Augenh. **48**:24, 1910; Ueber Beziehungen der Gefasshaut zu endokrinen Störungen, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **48**:26, 1930.

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to the causative agent of herpes or sympathetic ophthalmia. In Salus' case grayish nodules were present in the iris, and he performed an iridectomy to relieve increased intraocular pressure, but he did not report an examination of the excised iridic tissue. Givner [11] did report on the excised iridic tissue and observed evidence of chronic inflammation with an occasional eosinophil. Wexler's [12] case was unique in that the vitiligo developed in a Negro woman and was extensive, but there was no complete laboratory examination.

The two recent attempts to isolate a virus, by Givner and by Hague,[13] both proved to be fruitless, as did the attempt in this case. The answer may lie in the fact that the material is taken from the patients too late in the course of the disease. In this case, the aqueous should have been used as soon as the retina began to look edematous, at least six weeks before it actually was used, and the same holds true for the spinal fluid. Hague's and Rone's [2] recent reports were all-inclusive and remarkable examples of thorough and painstaking clinical effort and literary research. The future advances lie in better and earlier methods of utilization of the pathologic fluid and tissue obtained from patients with this disease entity.

2 East Sixty-Ninth Street.

11. Givner, I.: Bilateral Uveitis, Poliosis and Retinal Detachment with Recovery, Arch. Ophth. **30**:331 (Sept.) 1943.

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LICHEN SCLEROSUS ET ATROPHICUS OF THE VULVA

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IT HAS been our observation that in the diagnosis of lesions of the vulva the disease known as lichen sclerosus et atrophicus has, in many cases, been overlooked and, second, that it has frequently been misdiagnosed and treated as leukoplakic vulvitis. The purpose of this paper is to describe the clinical and histologic features of lichen sclerosus et atrophicus and to show that it is an entirely distinct entity which should not be confused with leukoplakic vulvitis.

Lichen sclerosus et atrophicus is a rare disease of the skin, formerly classified as a variant of lichen planus, but now generally considered to be a disease entity belonging to the group of sclerotic atrophies. The dermatologic aspects of the disease have long been well established, but it has been only in the past fifteen years that the frequency and importance of the involvement of the vulva have been recognized.

The involvement of the vulva and perianal region is usually, but not always, associated with the typical cutaneous lesions. The disease presents itself in the anogenital region as a primary sclerotic atrophy in much the same fashion as on the skin except that the individual small white papule is not as much in evidence. The striking whiteness of the lesions is probably the reason for confusing it with leukoplakia, and the atrophy may resemble kraurosis or senile atrophy of the vulva.

In 1934, Montgomery and his co-workers,[1] in a paper on lesions of the vulva, distinguished kraurosis from leukoplakic vulvitis both on clinical and histologic grounds. They mentioned lichen sclerosus et atrophicus in the differential diagnosis, but did not discuss it. Kraurosis vulvae is described as a progressive atrophy of the mucous membranes of the vulva. They stated that the atrophic process rarely extends to the labia majora, to the perianal skin or to the outer surfaces of the thighs.

Leukoplakia of the vulva, on the other hand, is a hypertrophic process with thickening of the skin or mucous membranes. It occurs

From the Department of Dermatology and Syphilology, State University of Iowa Hospitals.

1. Montgomery, H.; Councellor, V. S., and Craig, W. McK.: Kraurosis, Leukoplakia and Pruritus Vulvae, Arch. Dermat. & Syph. **30**:80 (July) 1934.

as single or multiple discrete plaques on the inner surfaces of both labia, the perineum, the clitoris and the vaginal mucosa. Occasionally there may be diffuse involvement of all these areas. These authors stated that, in their experience, leukoplakia did not extend to the outer surfaces of the labia majora or to the perianal skin.

The histologic picture of kraurosis, as described by Montgomery and his associates,[1] consists of relative and absolute hyperkeratosis, either no change in the stratum granulosum or increase in the number of cell layers, decided atrophy of the prickle cell layer and liquefaction necrosis of the basal cell layer. There is an area of edema just beneath the epidermis, with edema and homogenization of the connective tissue fibers, obliteration of the rete ridges and a diffuse or perivascular infiltrate in the middle layer of the cutis.

Leukoplakia of the vulva presents an entirely different histologic picture. It is a hypertrophic process with hyperkeratosis, increase in the stratum granulosum, acanthosis and relatively little infiltrate or change in the cutis.

We agree with Montgomery and his colleagues [1] that leukoplakia of the vulva and kraurosis vulvae can and should be distinguished from each other on the aforementioned grounds. However, there seems to be a decided tendency on the part of many physicians to overlook the disease known as lichen sclerosus et atrophicus, as it occurs on the vulva, and to confuse it with leukoplakia. This situation, we feel, is a serious one, not only on theoretic grounds, but because the treatment of the two diseases is so different. Since leukoplakia is known to be a precancerous disease, usually requiring vulvectomy, it is imperative to distinguish it from lichen sclerosus et atrophicus which, as far as we know, does not eventuate in malignant disease.

REVIEW OF LITERATURE

The clinical entity now known as lichen sclerosus et atrophicus was first described by Hallopeau [2] in 1887. Hallopeau expressed the opinion that it was a special form of lichen planus. This conception of the disease was still held in 1910, at which time Ormsby [3] reviewed the literature and reported 5 new cases. Ormsby stated that in the cases reported since Hallopeau's original case there had been lesions noted about the vulva. One of the cases which Ormsby reported showed typical "lichen planus sclerosus" on the vulva, especially about the clitoris.

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2. Hallopeau, H.: Leçens clinique sur les maladies cutanées et syphilitiques, Union méd. **43**:742 (May) 1887; abstracted, Ann. de dermat. et syph. **8**:790, 1937.

3. Ormsby, O. S.: Lichen Planus Sclerosus et Atrophicus (Hallopeau): A Report of Six Cases (Five New) with a Review of the Literature, J. A. M. A. **55**:901 (Sept. 10) 1910.

A case was recorded in 1910 by Dreuw [4] as scleroderma conscripta with a question mark. The patient was a woman, aged 49, who had on the upper portions of the trunk white areas made up of smaller white spots varying in size from that of a pinhead to that of a pea, which were round or oval, white and only slightly elevated and had on their surfaces horny scales probably corresponding to the follicular orifices. In addition to these lesions she had what was called kraurosis vulvae.

Hoffmann [5] reported 2 cases in 1914 of "lichen sclerosus" involving the vulva. The first case was in a woman, aged 45, who had typical extragenital lesions of lichen sclerosus et atrophicus and symmetric lesions on the vulva, which extended from the inguinal region and upper part of the thigh on each side to involve both the labia majora and the labia minora. Sections taken from the area between the labium majus and labium minus showed the typical sclerotic atrophy of lichen sclerosus et atrophicus. The second case was similar, but not as typical as the first.

In 1915, Montgomery and Culver [6] reported a case of "lichen sclerosus vulvae." The patient was a woman, aged 52, with lesions on the back, sides of the neck, chest, extensor surface of the right arm and vulva. The changes on the vulva were described as "leucoplasia-like" patches, especially on the inner surfaces of the labia minora. There was also involvement of the perianal skin. Comedo-like plugging is mentioned in connection with the extragenital lesions. The histologic picture showed hyperkeratosis and acanthosis. The connective tissue in the upper part of the cutis was "dull and cloudy." There was no infiltrate characteristic of lichen planus.

Ormsby and Mitchell [7] presented a case before the Chicago Dermatological Society in 1922, with a diagnosis of "lichen atrophicus et sclerosus and kraurosis vulvae." The patient had a typical patch of lichen sclerosus et atrophicus on the left side of the neck and identical lesions on the vulva.

In 1933, Madden [8] presented a case before the Minnesota Dermatological Society, with the diagnosis of "kraurosis vulvae." In the discussion of the case Michelson [9] favored the diagnosis of lichen planus

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4. Dreuw: White Spot Disease oder Sclerodermia Circumscripta? Dermat. Stud. **21**:214, 1910; cited by McKee, G. M., and Wise, F.: White Spot Disease, J. Cutan. Dis. **32**:639 (Sept.) 1914.

5. Hoffmann, C. A.: Ueber Lichen sclerosus der weiblichen Genitalien, Dermat. Ztschr. **21**:32 (June) 1914.

6. Montgomery, D. W., and Culver, G. D.: Lichen Sclerosus Vulvae, J. Cutan. Dis. **33**:572 (Aug.) 1915.

7. Ormsby, O. S., and Mitchell, J. H.: Lichen Planus Atrophicus et Sclerosis and Kraurosis Vulvae, Arch. Dermat. & Syph. **5**:786 (June) 1922.

8. Madden, J. F.: Kraurosis Vulvae, Arch. Dermat. & Syph. **29**:442 (March) 1934.

9. Michelson, in Montgomery.[10]

with atrophy, but Montgomery [10] felt that the clinical picture and histologic structure were those of lichen sclerosus et atrophicus.

In 1934, 2 patients were presented before the Chicago Dermatological Society with the question as to whether lichen sclerosus et atrophicus of the vulva was present. In the first case, presented by Mitchell,[11] the diagnosis was questionable. The second case, presented by Finnerud and Wolff,[12] was that of a woman, aged 76, in whom the skin of the anogenital region was symmetrically involved in a white atrophic process which extended back to the sacral region along the intergluteal folds. Michelson,[13] in the discussion, called attention to the fact that sometimes cases which are diagnosed as kraurosis vulvae are in reality lichen sclerosus et atrophicus.

Madden [14] presented 2 additional cases of lichen sclerosus et atrophicus involving the vulva, 1 in 1936 and another in 1937, before the Minnesota Dermatological Society.

In 1938, 4 patients were presented before the Atlantic Dermatologic Conference, with sclerotic atrophic lesions of the vulva.[15] In 3 of these patients the vulvar lesions were accompanied by white atrophic cutaneous lesions. All the cases were presented with the diagnosis of circumscribed scleroderma alone or accompanied with kraurosis or leukoplakia of the vulva. In the discussion of these cases, only Stokes and Goodman [16] suggested the diagnosis of lichen sclerosus et atrophicus, which seems to be the correct one rather than the diagnosis under which the patients were presented.

In 1940, Montgomery and Hill [17] published their classic paper on lichen sclerosus et atrophicus. Among the 38 cases in women which

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10. Montgomery, H., in discussion on Madden, J. F.: Kraurosis Vulvae, Arch. Dermat. & Syph. **29**:442 (March) 1934.

11. Mitchell, J. H.: Lichen Planus Atrophicus et Sclerosus; Shamberg's Disease; Vitiligo, Arch. Dermat. & Syph. **31**:141 (Jan.) 1935.

12. Finnerud, C. W., and Wolff, M. J.: Lichen Planus Atrophicus? Kraurosis Vulvae? Arch. Dermat. & Syph. **31**:142 (Jan.) 1935.

13. Michelson, H. E., in discussion on Finnerud and Wolff.[12]

14. Madden, J. F.: Kraurosis Vulvae: Lichen Sclerosus et Atrophicus, Arch. Dermat. & Syph. **35**:1182 (June) 1937; Case for Diagnosis (Lichen Sclerosus et Atrophicus? Kraurosis Vulvae?), ibid. **37**:720 (April) 1938.

15. (*a*) Ginsburg, L.: Circumscribed Scleroderma or Leukoplakia of the Vulva in a Child Aged Eight Years, Arch. Dermat. & Syph. **39**:903 (May) 1939; (*b*) Circumscribed Scleroderma (White Spot Disease): Leukoplakia of the Vulva, ibid. **39**:903 (May) 1939. (*c*) Ketron, L. W., and Ellis, F. A.: Kraurosis Vulvae and White Spot Scleroderma, ibid. **39**:904 (May) 1939. (*d*) Bernstein, J. C., and Robinson, H. M.: Circumscribed Scleroderma, ibid. **39**:904 (May) 1939.

16. Stokes, J. H., and Goodman, M. H., in discussion on Ginsburg.[15a, b] Ketron and Ellis.[15c] Bernstein and Robinson.[15d]

17. Montgomery, H., and Hill, W. R.: Lichen Sclerosus et Atrophicus, Arch. Dermat. & Syph. **42**:755 (Nov.) 1940.

they reported, there was involvement of the vulva in 20. Since then, and in a great part because of this paper, lichen sclerosus et atrophicus has been generally accepted as a distinct disease entity and the importance of the involvement of the anogenital region more widely recognized.

CLINICAL FEATURES

Lichen sclerosus et atrophicus occurs much more frequently in women than in men. Montgomery and Hill [17] observed, in the 46 cases which they reviewed, that it occurred six times as often in women. The age of onset may vary from 2 years [15a] to 63 years,[3] with many more cases occurring later in adult life.

The disease is almost never limited to the vulva alone. In the 38 cases in women reported by Montgomery and Hill,[17] there were vulvar lesions exclusively in only 3, and in the 17 patients we studied, only 1 woman did not show lesions in other areas. In almost every case, lesions will be seen extending to the perianal skin, and it is the unusual patient in whom lesions cannot be seen elsewhere on the body. In the cases reported by Montgomery and Hill,[17] 6 of the 38 women did not show lesions outside the anogenital region, and in our 17 cases, we were unable to demonstrate lesions elsewhere in 5 cases. These extragenital lesions are most often seen on the upper part of the trunk, on or beneath the breasts and over the clavicles, shoulders, upper part of the back, neck and forearms. The most frequently observed symptom is mild pruritus.

Unlike many other diseases of the vulva, lichen sclerosus et atrophicus has an elementary or characteristic cutaneous lesion, which fact should be of great value in the differential diagnosis. The elementary cutaneous lesion is a small discrete irregular often polygonal flat-topped white papule. The color of the lesion is striking and has been described as ivory or "mother of pearl." [3] The papules may be slightly elevated and vary in size from that of a pinhead to that of a split pea.

The papules show a tendency toward grouping, and as the disease progresses they may coalesce to form plaques. The outline of the individual papule in the plaque, however, can usually be made out. As the lesions become older, a white "parchment-like" or "tissue-paper-like" wrinkling is often seen.[3]

The older papule usually has on its surface one or several black horny comedo-like plugs. This plugging is not always seen clinically, but without exception is recognizable on histologic examination.[17]

The disease is chronic in its course, persisting for many months or years. However, the lesions sometimes undergo resolution, leaving a delicate smooth white soft atrophic area the size and shape of the original lesion.[3] We have been unable to find a single case reported in the literature of epithelioma arising from lichen sclerosus et atrophicus.

When lichen sclerosus et atrophicus involves the vulva, it shows all the characteristic features just described. In the typical case, as one examines this region one sees a plaque of white wrinkled atrophic tissue which involves, in a continuous and symmetric fashion, the entire vulva, including the labia majora, and extends, without interruption, around the anal orifice for a distance of about 3.5 cm. in a fan-shaped design. This plaque is a peculiar white and is sharply outlined from the surrounding normal skin at the periphery. There is no thickening of the tissue, the involved area being either only slightly elevated or level with the surrounding skin. The individual papules are most easily seen on the skin around the anus, where they tend to occur in lines radiating outward from the anal orifice, like the spokes of a wheel. On close observation one may see on the surface of these papules black keratotic points or minute depressions, where the horny material has dropped out leaving a pit.

HISTOLOGIC FEATURES

The histologic picture of lichen sclerosus et atrophicus according to Montgomery and Hill [17] is surprisingly constant, despite the age of the patient or the situation of the lesion. In the 17 patients with lichen sclerosus et atrophicus whom we have studied, we have performed eight vulvar biopsies and four biopsies of skin. In all these cases the histologic observations were consistent with the following description. The changes in the epidermis are as follows: thickening of the stratum corneum (hyperkeratosis) with horny plugging of the hair follicles and sweat duct openings and atrophy of the prickle cell layer with disappearance of the rete pegs and papillae. Just below the basal cell layer, in the papillary and subpapillary layers of the dermis, is a sharply defined band of tissue which stains poorly. There are few connective tissue nuclei in this band of tissue and practically no cellular infiltrate. and the connective tissue in this zone is seen to be felted and homogenized. This area of sclerosis may vary in width, but it is invariably present, and the elastic tissue is absent at this level. There is a perivascular or diffuse infiltrate of chronic inflammatory cells in the middle part of the cutis, beneath the aforementioned band. No obliterative changes are seen in the deeper blood vessels.

In our 17 patients with lichen sclerosus et atrophicus, 16, or all but 1, had lesions of the vulva. The diagnosis was confirmed by biopsy of eight of these vulvar lesions. All but 1 of the patients with lichen sclerosus et atrophicus of the vulva showed extension to the perianal region, and, in 11 of the 16, typical lesions of the disease were demonstrated elsewhere on the skin. The diagnosis of the cutaneous lesions was confirmed by biopsy in 4 cases.

Nine of the patients were referred to us by gynecologists, 4 by general practitioners, 2 by internists, 1 by another dermatologist and 1 by a surgeon.

In 2 of the cases referred to us by gynecologists, the patient was subjected to a vulvectomy in spite of the fact that we assured the referring physician that the lesion was not precancerous. A third patient was also subjected to a vulvectomy. After her operation she was referred to us because of aggravation of the same symptoms for which she was seen originally, that is, itching and dyspareunia. Examination revealed the fan-shaped area of whiteness and atrophy surrounding the anal opening to be still present, although the vulva had been removed.

We wish to present the following 3 cases as illustrative of those we have seen.

REPORT OF CASES

CASE 1.—H. P., a white woman, was first seen at the University Hospitals at the age of 42, with the complaint of profuse vaginal bleeding, for which a vaginal hysterectomy was performed. She was not seen again until twelve years later, at the age of 55, when she came to the Dermatology Clinic because of mild pruritus of the vulva present off and on for eighteen years. She had noticed white patches on her shoulders for one year.

Over the shoulders and at the root of the neck were seen several white plaques made up of thin "cigaret-paper-like" skin. The plaques varied in size from 3.5 to 7 cm. in diameter. Over the surface of each plaque were seen many black horny comedo-like plugs. At the periphery of each plaque, small white polygonal "mother of pearl" papules could be made out, separated from each other by apparently normal skin.

The entire anogenital region, including the introitus, the labia minora, the inner surfaces of the labia majora and the skin surrounding the anus, showed whiteness, atrophy and wrinkling, resembling the lesions on the shoulders and at the root of the neck. Although the keratotic plugging was not as much in evidence as it was in the cutaneous lesions, the elementary papule could be seen at the outer margins of the vulvar lesion. The symmetric configuration and sharp demarcation of the lesion were remarkable. The clinical appearance closely resembled that in case 2 (fig. 1), but was not as pronounced. There were no lesions in the mouth.

Sections from the right labium minus showed moderate hyperkeratosis. The prickle cell layer was approximately normal in thickness, but the rete pegs were absent. In the upper third of the cutis, there was a band of tissue which was sharply outlined at its lower border from the tissue below. This band of tissue stained poorly and was practically devoid of either connective tissue nuclei or inflammatory cells. The connective tissue in this area was felted and homogenized. There were many dilated capillaries throughout the entire cutis, but little inflammatory infiltrate. The elastic tissue was absent throughout the entire section except around one small arteriole.

The patient returned to the clinic on several occasions. For the first fourteen months after the diagnosis was made, new lesions continued to appear on the back and the lesions on the shoulders enlarged peripherally. The last time the patient was seen, which was twenty-six months after her first visit, there was definite regression of the lesions on the vulva and the plaques on the back and at the root of the neck were less clearly defined.

CASE 2.—B. R., a white woman, was first seen by the Department of Dermatology of the University Hospitals at the age of 71, because of itching of the anogenital region for five years. She had been seen the year previously by the Department of Gynecology and given a diagnosis of kraurosis vulvae.

The skin and mucous membrane of the anogenital region showed continuous and almost perfect symmetric involvement, which extended from about 5 cm. above the clitoris, down the outer margin of the labia majora and posteriorly around the anus in a semicircle to involve the intergluteal fold for a distance of about 5.5 cm. (fig. 1). The tissue in this area was white, atrophic and wrinkled and contrasted sharply in both color and consistency with the skin at the periphery. There

Fig. 1 (case 2).—Typical lichen sclerosus et atrophicus involving the vulva and perianal region, with the characteristic white atrophic area sharply outlined from the surrounding skin in a symmetric fashion. The individual small white papule with keratotic plugging can be seen best at the periphery of the fan-shaped lesion surrounding the anal opening.

were no elevated plaques or thickened areas. At the outer margin of the semicircular lesion around the anal opening, the small individual papules making up the plaque were easily demonstrated. Many of these papules showed either minute black points or depressions. No other cutaneous or oral lesions were seen.

Sections from the periphery of the area posterior to the anus showed hyperkeratosis, decrease in the number of cells of the rete mucosum and disappearance of

the rete pegs (fig. 2). The collagenous connective tissue in the upper third of the cutis was almost structureless, except for a few fine fibrils, and took a faint pink stain with hematoxylin and eosin. This band of tissue was practically devoid of elastic fibers. Collections of small round cells were seen in the lower portions of the cutis.

CASE 3.—C. V., a white woman aged 52, was first seen at the University Hospitals on Jan. 12, 1944. She came to the hospital because of white patches on the inner aspect of the thighs, which she had noticed for six months. These lesions were completely asymptomatic. Her menopause had occurred at the age of 51. The past menstrual history was noncontributory. She had a cervical polyp removed at another hospital five years previously.

On examination three white plaques were seen on the inner surfaces of the upper third of the thighs (fig. 3). The single oval plaque on the inner aspect of the left thigh measured approximately 5 cm. in diameter. Almost exactly

Fig. 2 (case 2).—Lichen sclerosus et atrophicus. Section from the periphery of the area posterior to the anus (Weigert's elastic tissue stain counterstained with hematoxylin and eosin, × about 103), showing hyperkeratosis, atrophy of the prickle cell layer, loss of rete pegs, the characteristic band of poorly staining, felted and homogenized connective tissue in the upper part of the cutis, loss of elastic tissue in this area and collections of small round cells in the portion of the cutis below.

opposite this lesion, on the inner surface of the right thigh, was a lesion similar in both size and shape. Another larger plaque was seen on the right, irregular in contour and about 10 by 5 cm. in its greatest dimensions. This plaque was above and lateral to the smaller lesion (patient in lithotomy position). The skin over these plaques was white, wrinkled and atrophic in appearance.

Beginning at the posterior commissure and extending back toward the anal opening in a symmetric fashion, the skin showed whiteness and atrophy (fig. 3). At the periphery of the lesion in the perianal region, individual white pea-sized atrophic papules were seen. The other portions of the vulva showed no clinically recognizable changes. There were no other cutaneous or oral lesions.

The patient was seen again on June 21, 1946, and at that time the lesions had neither progressed nor regressed and were still asymptomatic.

Sections from the area of diffuse whiteness at the posterior commissure showed relative and absolute hyperkeratosis and decided atrophy of the rest of the epidermis, with almost complete loss of the rete pegs (fig. 4). The junction of the epidermis and dermis was seen only as a slightly wavy line. One area showed keratotic plugging of the pilosebaceous apparatus. In the papillary and subpapillary layers of the dermis was a wide band of tissue, which was composed of finely fibrillar, poorly staining homogenized collagen fibers with few nuclei and no inflammatory cells. The dermis below this band of tissue revealed a moderate diffuse and perivascular infiltrate of chronic inflammatory cells. There was no change in the deeper blood vessels. The elastic tissue was absent from the upper third of the cutis.

Fig. 3 (case 3).—Lichen sclerosus et atrophicus of the vulva and perianal region, with typical extragenital cutaneous lesions on the inner aspect of the thighs and showing the symmetric whiteness at the posterior commissure, which extends backward to surround the anal opening. The plaques on the thighs show the "tissue-paper-like" wrinkling of the white atrophic skin.

LEUKOPLAKIC VULVITIS

The term leukoplakia is taken from the Greek and literally means white plate. It has been applied to any and all of the diseases of the vulva which clinically show whiteness. It has been used to describe kraurosis, lichen planus, lichen sclerosus et atrophicus, simple senile atrophy of the vulva, pruritus with lichenification, true leukoplakia and even vitiligo. Several authors have recently attempted to correct this situation. We have particular reference to the articles of Montgomery

and his associates [1] in 1934 and Savill [18] in 1940. Savill adequately summed up the situation as follows:

"This term [leukoplakia vulvae] has been widely and wrongly used to describe the condition with superficial, white, sodden, hyperkeratotic epithelium, extensive or in patches, which is seen with several forms of skin disease. True leukoplakia is very rare. It resembles the patches seen on the tongue—translucent bluish-white or gray streaks or patches with edges sometimes abrupt, sometimes fading to the normal. Or it may have thickened raised white patches with a sinuous border, which may spontaneously become detached at long intervals and soon renewed."

Fig. 4 (case 3).—Lichen sclerosus et atrophicus. Section from the posterior commissure (hematoxylin and eosin, × about 106), showing hyperkeratosis, atrophy of the rest of the epidermis and the characteristic felting of the connective tissue of the upper third of the cutis.

We heartily agree with the views of those who wish to limit the term leukoplakia vulvae or leukoplakic vulvitis to a distinct clinical and histologic entity.

True leukoplakia is a "neoplastic" disease of the mucous membranes of the mouth and external genitals. We use the term "neoplastic" in contradistinction to the word "inflammatory." It is primarily a disease of the epidermis, the changes in the cutis being comparatively minimal and secondary to the epidermal changes. Leukoplakia may develop in

18. Savill, A.: Treatment of Pruritus Vulvae, Leukoplakia and Kraurosis, Brit. J. Dermat. **52**:321 (Nov.) 1940.

tissue changed by syphilis, chronic irritation or other diseases, but may be independent of any of these. It is seen more commonly in older persons, just as senile keratoses of the skin appear in persons in the older age group. As Ormsby and Montgomery suggested, leukoplakia might be regarded as senile keratosis of the mucous membranes.[19]

Clinical Features.—On the vulva, leukoplakia may appear as a single plaque or as several plaques located anywhere from the inner surfaces of the labia majora laterally to the vagina medially and from the clitoris above to the posterior commissure below. We agree with Montgomery that leukoplakia rarely extends to the outer surfaces of the labia majora or to the perianal skin.[1] If the plaques are multiple or if the involvement is diffuse rather than in plaques or lines, the distribution of the lesions is not strikingly symmetric as in lichen sclerosus et atrophicus.

The stria or plaque is white or bluish white. The lesion may be sharply defined from the surrounding tissue or may merge gradually with it. On palpation there is thickening and elevation above the adjacent tissue. This thickening is a progressive affair—the older the lesion, the greater the thickening. Fissures and ulceration are common in the older lesion.

There is no elementary polygonal flat-topped papule and no keratotic plugging as there is in lichen sclerosus et atrophicus. There may be accentuation of the normal lines of cleavage, but not the typical "tissue-paper-like" wrinkling which is so characteristic of lichen sclerosus et atrophicus. There are no associated lesions elsewhere on the body in leukoplakia as in lichen sclerosus et atrophicus. Attention has previously been drawn to the occurrence of senile keratoses in patients in the same age group as those suffering from leukoplakia. However, senile keratosis would indeed be difficult to confuse with the extragenital lesions of lichen sclerosus et atrophicus.

While the course of lichen sclerosus et atrophicus is chronic and prolonged, the lesions may remain static over long periods or may actually regress. This is not the case in leukoplakia. It is a constantly progressive disease which eventuates in an epithelioma, unless the patient's life is terminated by some other cause or unless the lesion is treated adequately. The rate of progression is, of course, variable, the malignant change occurring at times many years after the onset of leukoplakia.

Histologic Features.—The histologic picture in leukoplakia shows increase in all the layers of the epidermis, with decided hyperkeratosis and irregular acanthosis, resulting in an increase in size and length of the rete pegs. There may be areas in the section which show ulceration

19. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6. Philadelphia, Lea & Febiger, 1943, p. 751.

of the epitheliuni. In these areas the surface is usually covered by a crust of fibrin and leukocytes. The cutis may show little or no change, but in most cases there is a moderate to decided diffuse infiltrate of chronic inflammatory cells in the upper portion. Where the hypertrophy of the epidermis is greatest there may be atrophic changes in the subpapillary layer of the cutis, accompanied by loss of elastic tissue.

Our experience with leukoplakia of the vulva is limited to approximately 4 cases, because these patients are seldom referred to us.

We wish to report the following case as an example of true leukoplakia of the vulva.

REPORT OF A CASE

CASE 4.—B. M., a white woman aged 53, was first seen at the University Hospitals on March 24, 1943, because of itching of the vulva for one year and

Fig. 5 (case 4).—Leukoplakia of the vulva, showing whiteness and thickening involving the vulva from the inner surface of the labia majora to the vagina and from the clitoris to the posterior commissure, but not beyond, in the perianal region. The absence of the "tissue-paper-like" wrinkling and the small individual papule characteristic of lichen sclerosus et atrophicus are evident.

whiteness of the vulva for three years. She had had two children, and her menopause had occurred at the age of 48. The past medical history was noncontributory, and the general physical examination failed to reveal abnormalities.

On examination of the external genitals, the inner surface of the labia majora, both surfaces of the labia minora, the clitoris and the introitus as far back as the posterior commissure were seen to be white and thickened (fig. 5). Both the whiteness and the thickening were much greater at the upper and central portions, that is, on the labia minora and clitoris. The thickened tissue was definitely palpable to the examining finger. There was no change in the perianal skin, and no other cutaneous or oral lesions were seen. The results of the remainder of the pelvic examination were essentially negative.

On April 3 a simple vulvectomy was done. Sections through the upper portion of the vulva revealed decided thickening of the epidermis, in which the stratum corneum and prickle cell layer were particularly prominent (fig. 6). The acanthosis produced by the increase in the rete mucosum was moderate and irregular. The basal cell layer was intact. The number of cells constituting the epidermis varied considerably from one portion of the section to another, but in no area could there be said to be atrophy. Where the hyperkeratosis and acanthosis was most extreme, the papillary and subpapillary layers of the cutis showed poorly staining and homogenized connective tissue. The elastic tissue in these areas was absent. Throughout the entire section there was an increase in number and dilatation of the vessels in the subpapillary layer of the cutis. There was a moderate perivascular and, in some areas, diffuse infiltrate of chronic inflammatory cells in the upper third of the cutis. In many places this infiltrate was heaviest immediately below the thickened epidermis.

Fig. 6 (case 4).—Leukoplakia of the vulva. Sections through the upper portion of the vulva (hematoxylin and eosin, × about 99), showing the decided hyperkeratosis and moderate irregular acanthosis, with minimal changes in the cutis consisting of dilatation of the superficial blood vessels and a moderate infiltrate of chronic inflammatory cells. At the extreme right is an area of poorly staining homogenized connective tissue.

SUMMARY AND CONCLUSIONS

Lichen sclerosus et atrophicus is a rare disease of the skin, belonging to the group of sclerotic atrophies. It is much commoner in women than in men, and the vulva is now known to be one of the sites of predilection of the disease.

Because of the whiteness of the vulvar lesions, lichen sclerosus et atrophicus is frequently confused with leukoplakic vulvitis. Lichen sclerosus et atrophicus of the vulva may be distinguished clinically from

leukoplakia by the characteristic plaque of strikingly white wrinkled atrophic skin and mucous membrane covering the entire vulva and perianal region in a continuous and symmetric fashion, sharply outlined from the surrounding normal skin, and by the elementary lesion, a small individual flat-topped white papule which may have on its surface several black comedo-like plugs. Lesions elsewhere on the body are almost always seen.

We feel that the term leukoplakia should be reserved for a hypertrophic precancerous disease of the mucous membranes, characterized by whiteness and thickening, which may occur in lines, plaques or diffusely. On the vulva there is seldom extension of this process to the perianal skin, and no lesions are observed elsewhere on the body.

Lichen sclerosus et atrophicus may be differentiated from leukoplakia on histologic grounds, the former showing hyperkeratosis, atrophy of the rest of the epidermis and a peculiar sclerotic change in the connective tissue just beneath the epidermis, with loss of elastic tissue in the zone, while the latter shows increase in all layers of the epidermis, with minimal and secondary changes in the cutis.

From the group of 17 cases of lichen sclerosus et atrophicus which we have studied, we have reported 3 which we feel are typical. A typical case of leukoplakia is also presented.

In our opinion it is important that the two diseases, lichen sclerosus et atrophicus and leukoplakia, be correctly diagnosed, because the first is a benign lesion and the second a known precancerous lesion for which vulvectomy is usually required.

SURGICAL MANAGEMENT OF ONYCHAUXIS AND ONYCHOGRYPOSIS

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THE TREATMENT of the diseases of the nails has long been relegated to dermatologists. General practitioners and general surgeons give little thought and less consideration to these problems, unless the complaints of the patient are so vociferous as to demand some sort of definitive treatment. Then the patient is either referred to a dermatologist or the offending nail plate is merely excised, with the hope and expectation that the new nail, when it grows, will possess a normal appearance. Adequate treatment can go much further to insure a satisfactory result than the heretofore haphazard methods.

Onychauxis and onychogryposis are dystrophic diseases of the nail in which the nail plate becomes decidedly hypertrophied. The differentiation of the two entities is only one of degree of severity. In onychauxis the nail plate becomes greatly thickened. There may be noted some deformity or distortion of the nail. However, in onychogryposis the hypertrophy is so extensive that a horny process extends from the nail. In old cases these horny projections may become long and curved.

The cause of these diseases is not clearly understood. In the large majority of cases, there is a definite history of trauma. The trauma may be in the nature of mild persistent insult to the nail or sudden severe injury. The slow mild, rather chronic, type of irritation may occur on the finger nails from the use of tools or in the toe nails from the persistent wearing of short tightly fitted shoes. The presence of these changes in the toe nails of persons who persistently go barefoot fortifies the belief in the importance of trauma as the causative factor. In England onychauxis is afforded the common name of "hostler's toe," because of the frequent occurrence in men who tend horses and whose toes are often stepped on by the animals. Any injury or irritation of the nail over a long period of time may produce hypertrophy of the injured nail. The same condition may arise following severe sudden injury. This may arise from the dropping of heavy objects on the fingers or the toes. The striking of a finger with a hammer has stimulated the onset of hypertrophic changes.

In some cases the hypertrophy noted in the nails is a manifestation of a general systemic disease. This is usually a peripheral trophic change, such as peripheral neuritis and peripheral stasis (noted in cardiac disease with decompensation). The hypertrophy of the nails is also associated with leprosy, ichthyosis, hemiplegia and tabes. In syphilitic patients, this disease bears the specific name of hypertrophic syphilonychia. Several of the cases reported in the literature suggest an endocrinopathy to be the causative agent (Hollander,[1] Alderson,[2] Lisser,[3] Block and Stauffer [4] and Combes [5]). This is usually a thyroid or pituitary deficiency. Touraine and Soulignac [6] have reported cases of familial onychogryposis.

Any disease that is not definitely of traumatic origin naturally requires therapeutic consideration. If there is residual hypertrophy of the nail following adequate treatment and relief of the general systemic disease, surgical correction is to be attempted.

The hypertrophied nail plate presents one of two problems. In the cases of milder disease a portion of the nail may be observed to be free of the hypertrophy. This may be present only in that portion of the nail along the lateral border protected by the sulcus matricis marginalis (fig. 1). If the surgeon can be assured, on gross examination, that hypertrophy is not present, this portion of the nail may be preserved. In the cases in which a small fringe of the nail may be preserved, a closer to normal breadth of nail may be expected. In spite of this fact, the surgeon should reject, without qualm, the full nail plate if there is any question in his mind as to the presence of hypertrophy. When the hypertrophied nail plate is removed, care must be taken to protect the matrix in every way possible. In some cases the matrix will be seen to be partially or fully supplanted by cicatrices. In such cases, the scar tissue must be removed. The excision may extend down

1. Hollander, L.: Onychauxis Due to Hypopituitarism, Arch. Dermat. & Syph. **2**:35 (July) 1920; Pituitary Gland Dystrophies, ibid. **7**:632 (May) 1923.

2. Alderson, H. E.: Onychauxis and Thyroid Therapy, Arch. Dermat. & Syph. **5**:602 (May) 1922.

3. Lisser, H.: Onychauxis in a Eunuchoid: Remarkable Improvement by Implantations of Testicular Substance, Arch. Dermat. & Syph. **10**:180 (Aug.) 1924.

4. Block, B., and Stauffer, H.: Skin Diseases of Endocrine Origin (Dyshormonal Dermatoses), Poikiloderma-Like Changes in Connection with Underdevelopment of Sexual Glands and Dystrophia Adiposogenitalis, Arch. Dermat. & Syph. **19**:22 (Jan.) 1929.

5. Combes, F. C.: Onychauxis and Keratosis Plantaris, Arch. Dermat. & Syph. **24**:711 (Oct.) 1931.

6. Touraine, A., and Soulignac: Onychogryphose congénitale et généralisée des orteils, Bull. Soc. franç. de dermat. et syph. **44**:305 (Feb.) 1937.

to the periosteum of the distal phalanx, if necessary. Although it is ideal to preserve all possible matrical tissue, it is of prime importance to prepare a smooth recipient bed for the nail graft. The presence of matrix is not essential for a good take.

The operative technic of nail grafting to be employed is a modification of the method described by Sheehan [7] in 1929. The recipient and donor digits are scrubbed with a brush, medicinal soft soap and water for a period of ten minutes, twenty-four hours prior to the operation. Much care is expended in the insurance of cleanliness about the free borders of the nails and the nail sulci. The cuticle is clipped short. Both digits are swathed in sterile dressings. In the operating room at the time of operation the lower portions of both extremities are thoroughly cleansed with medicinal soft soap and water. Special attention is again directed to the recipient and donor digits. The parts are then painted with antiseptic solution. The extremities are draped in sterile covers.

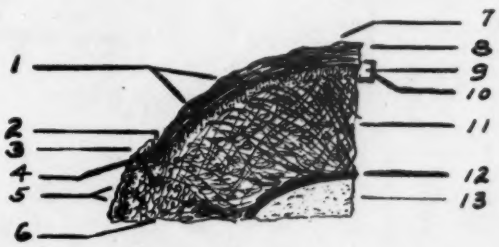

Fig. 1.—Diagrammatic quarter cross section of finger tip. *1*, cristae matricis unguis; *2*, sulcus matricis unguis; *3*, vallum unguis; *4*, margo lateralis unguis; *5*, cristae cutis; *6*, retinacula cutis; *7*, corpus unguis; *8*, stratum corneum unguis; *9*, stratum germinativum unguis; *10*, matrix unguis; *11*, retinaculum unguis; *12*, periosteum; *13*, phalanx.

The anesthesia is an elective consideration. Spinal anesthesia is excellent for the pedal extremities. Refrigeration anesthesia may be employed for either arms or legs. Local anesthesia of the block type (nerve or field) is useful, but local infiltration is not satisfactory. Naturally, any of the general anesthetics may be employed.

A tourniquet is applied to the extremity or to the individual digit. The hypertrophied portion of the nail or the whole nail is excised. If a portion of the nail is to be preserved, the nail plate is incised in an exactly perpendicular plane to its surface with a sharp scalpel down to the stratum germinativum unguis. The hypertrophied portion of the nail plate can then be raised by blunt dissection with a small pair of

7. Sheehan, J. E.: Replacement of Thumb Nail, J. A. M. A. **92**:1253 (April 13) 1929.

blunt-ended scissors. This dissection is commenced at the free border. If the whole nail plate is to be removed, this is effected with blunt dissection, as previously suggested. The nail plate is separated from its attachment at the sulci by cutting with scissors along the border of the nail plate. It may be necessary to incise the superficial wall of the nail sulcus at the proximal end in order to remove carefully that portion of the lunula that is involved. Two lateral incisions will be found helpful in the exposure of this proximal portion (fig. 2 *A*). If there is scarring of the matrix present, the cicatrix should be excised. This excision is naturally dictated by the extent of the cicatrix. However, the end result must present a smooth bed for the graft. The

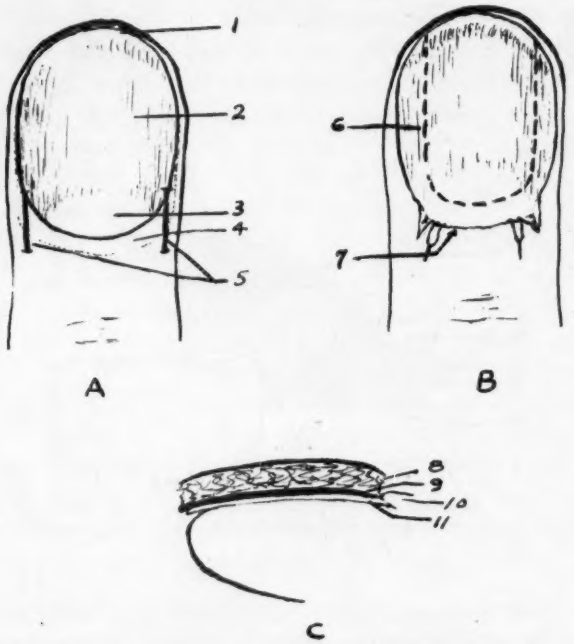

Fig. 2.—*A*, lines of incision of sulcus wall: *1*, free border of nail; *2*, corpus unguis; *3*, lunula, *4*; radix unguis and *5*, incisions. *B*, nail plate: *6*, line of incision in nail plate and *7*, retracted sulcus wall. *C*, pressure dressing: *8*, sponge rubber pad; *9*, tantalum sheet; *10*, sulcus wall (cuticle) and *11*, nail plate.

dissection may be carried as deep as just superficial to the periosteum of the distal phalanx. Bleeding is controlled with sponges soaked in hot saline solution. Clamps should not be used. The sponges are left in situ while the graft is prepared. The corresponding nail of the opposite extremity is selected for the donor of the graft. This selection is made because such a nail most nearly matches the original in structure, size and appearance. In the event of some exigency the graft donation is not restricted. Any other nail of any extremity may be used. The size

of the graft is laid out on the donor nail. The graft extends proximally, a little proximal of the middle of the lunula. A fringe of nail plate, approximately 2 to 3 mm., is preserved along the lateral borders to maintain support and position for the new outgrowth of nail (fig. 2 *B*). Usually it is necessary to incise the sulcus, as in figure 2 *A*, in order to expose the full extent of the nail desired. The nail plate is incised along the layout lines with a sharp scalpel. The nail is elevated from its matrix by blunt dissection with small blunt-ended scissors. Bleeding is controlled with sponges soaked in hot saline solution. A piece of tantalum sheet, about 0.015 inch (about 0.04 cm.) thick, is cut out and shaped to fit exactly the nail plate of the donor digit (fig. 2 *C*). This plate is held in place by a sponge rubber pressure bandage, which has been cut to the same pattern. The sponge rubber need not be of a greater thickness than ¼ inch (about 0.64 cm.).

The nail graft is coated with plasma paste (dried plasma and sterile water) on the fresh surface. The sponges are removed from the recipient area. The surface is now lightly coated with a solution of commercially prepared thrombin. The graft is placed with that portion of the lunula present on the graft well down into the proximal portion of the sulcus marginalis. The graft should fit the bed perfectly. The lateral sulci should be brought into approximation with the border of the nail graft. This procedure may create a slight narrowing of the new nail. However, if this is not effected, granulation tissue will occur, which will necessitate an increase in the period of convalescence, frought with innumerable silver nitrate cauterizations. The graft is held in place with the pressure dressing of tantalum sheet and sponge rubber, as described for the donor area (fig. 2 *C*). The tantalum sheet is cut about 1 mm. smaller than the nail graft. The pressure should be only sufficient to hold the graft in contact with its new bed. Too great a pressure will create ischemia of the subungual tissues and result in a nontake of the graft. Care must be taken to replace the tissue incised at the base of the nail. In most of the cases suturing is not necessary.

The after-care is rather simple. No dressings are performed until the tenth or the fourteenth day, unless there is an odor that suggests the presence of morbidity. If there are some granulations present at the time of dressing, they may be cauterized with a silver nitrate stick. The graft will appear dull and grayish near the free border, but at the proximal portion pinkness will demonstrate the viability of the graft. At subsequent dressings the free border must be kept clipped close to avert the nail's catching and injuring the delicate new nail formation. The donor nail will grow out surprisingly rapidly. If the tantalum sheet is maintained in position until the nail has reached the full extent of the matrix there will be little else required in the way of

dressing or other protection for the nail. The recipient area is maintained in dressings until the new nail has reached the full extent of the nail matrix also. In usually from three to four months both nails have fully regrown.

It will be noted that the process of nail grafting is synonymous with split skin grafting. Approximately the same layers of the skin are involved.

SUMMARY

A method of surgical management of onychauxis and onychogryposis by reconstruction of the nail plate with free nail grafting is described.

133 East Fifty-Eight Street (22).

Clinical Notes

RAT BITE FEVER CAUSED BY SPIRILLUM MINUS TREATED WITH PENICILLIN

Report of a Case

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Rat bite fever can be caused by either Spirillum minus (Spirochaeta morsus muris) or by Streptobacillus moniliformis (Haverhillia multiformis). Sodoku, or rat bite fever caused by S. minus, is produced only by the bite of a rat or other animal carrying the organism. On the other hand, infection with S. moniliformis may be caused by a rat bite or may follow the ingestion of contaminated food. This type of infection has also been called Haverhill fever.

Brown and Nunemaker [1] showed that the symptoms and course of the two diseases may be similar. However, Rosen and Denzer,[2] Larson [3] and Allbritten and his associates [4] have asserted that characteristic differential features exist. Allbritten and his associates summarized these differences in the following manner:

It appears that fevers caused by H. multiformis are characterized by arthritis and a small macular rash, as compared with rare involvement of the joints and a papular or large macular eruption when S. minus is concerned. When infection with H. multiformis has followed the bite of a rat there may be no exacerbation of the wound, leukocytosis is common and the period of incubation is apt to be brief.

The clinical picture of rat bite fever caused by S. minus is as follows: Following a bite by a rat there is an incubation period of one to four weeks. This is followed by an exacerbation of the original wound, with the local development of pain, swelling and bluish purplish discoloration. At this time a nodule or chancre-like ulcer may develop at the initial site. Regional lymphangitis and lymphadenitis are present. A generalized macular eruption develops. The lesions become purplish red, enlarge and form distinct erythematous indurated plaques in the skin.

The fever is of a remittent or intermittent type. Arthritis is usually absent. The laboratory observations are those of: polymorphonuclear leukocytosis, secondary anemia, a usually negative Wassermann reaction and a frequently positive Kahn reaction. Blood cultures are negative. The spirochetes may be seen in dark field

1. Brown, T. McP., and Nunemaker, J. C.: Rat Bite Fever: A Review of the American Cases with Reevaluation of Etiology; Report of Cases, Bull. Johns Hopkins Hosp. **70**:201 (March) 1942.

2. Rosen, E., and Denzer, B. S.: Rat Bite Fever Caused by Streptobacillus Moniliformis, J. Pediat. **24**:544 (May) 1944.

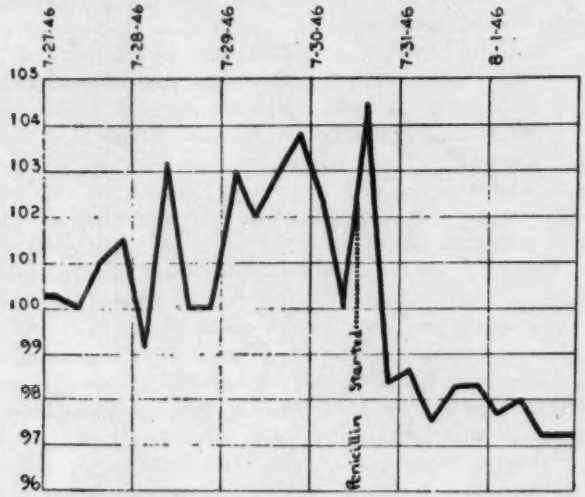
3. Larson, C. L.: Rat Bite Fever in Washington, D. C., Due to Spirillum Minus and Streptobacillus Moniliformis, Pub. Health Rep. **56**:1961 (Oct. 3) 1941.

4. Allbritten, F. F.; Sheely, R. F., and Jeffers, W. Z.: Haverhillia Multiformis Septicemia: Etiologic and Clinical Relationship to Haverhill and Rat Bite Fevers, J. A. M. A. **114**:2360 (June 14) 1940.

examination of the fluid from the local lesions or from material from infected lymph glands. For a conclusive diagnosis of the disease intraperitoneal or intracutaneous injection into the genitals of guinea pigs is required, with the subsequent recovery of S. minus.

Infection by S. minus has responded well in the past to arsenical therapy, particularly to arsphenamine and sulfarsphenamine. Although there have been several recent reports in the literature [5] as to the value of penicillin in rat bite fever caused by S. moniliformis, there are, insofar as a review of the literature discloses, only two reports [6] on the clinical use of penicillin in rat bite fever caused by S. minus.

We report a case of rat bite fever caused by S. minus which was treated with penicillin.



Temperature curve before and after institution of penicillin therapy

REPORT OF A CASE

N. J. O., 6 months old, was admitted to the hospital July 26, 1946. Five weeks prior to admission the child was bitten on the right wrist by a rat. There were four puncture marks on the wrist, which healed slowly. Ten days after the child was bitten the original wound swelled up, and a hard bluish nodule developed. The child was seen by a local physician, who prescribed sulfadiazine by mouth for two days. Two weeks later a generalized eruption of purplish red circinate lesions developed. She had been irritable and cranky for the past week, and the mother stated that the child had occasional fever.

5. (*a*) Brooksaler, F.: Penicillin Therapy in Rat Bite Fever, J. Pediat. **27**: 442 (Nov.) 1945. (*b*) Altemier, W. A.; Snyder, H., and Howe, G.: Penicillin Therapy in Rat Bite Fever, J. A. M. A. **127**:270 (Feb. 3) 1945. (*c*) Wheeler, W. E.: Treatment of Rat Bite Fever with Penicillin, Am. J. Dis. Child. **69**:215 (April) 1945.

6. Wheeler.[5c] Swyer, G. I. M.: Rat Bite Fever Due to Cat Bite: Satisfactory Response to Penicillin After Failure of Arsenotherapy, Brit. M. J. **2**:386 (Sept. 22) 1945.

On physical examination the baby appeared acutely ill. The temperature on admission was 100 F. The pharynx was red and injected. The examination revealed the chest to be normal, and there was no adenopathy or splenomegaly. On the right wrist there were four distinct puncture marks, with no induration or edema.

Scattered over the face, body and extremities there were many circinate erythematous lesions measuring from 2 to 5 cm. The lesions were purplish red and had definite well defined borders, and many of the lesions were clear in the center and contained a second circinate lesion within, giving the appearance of a target. There was a total of ten to twelve lesions.

The urine showed a trace of albumin. Examination of the blood revealed a total white cell count of 15,600 cells per cubic millimeter, with 90 per cent polymorphonuclear leukocytes, 8 per cent monocytes and 2 per cent eosinophils. The hemoglobin was 35 per cent, and the red blood cells totaled 2,800,000. The Wassermann reaction of the blood was negative. The sedimentation rate was 45 mm. in thirty minutes.

The temperature rose daily, reaching 103 to 104 F., and on the third day the child was given 0.01 Gm. of sulfarsphenamine intramuscularly. The following day, since no response was obtained, she was given penicillin, 5,000 units intramuscularly every three hours. This was continued for seven days. The response was dramatic. Within six hours after treatment with penicillin was started the temperature returned to normal and remained so. The following day the skin was completely clear of all lesions. The leukocyte count returned to normal. The sedimentation rate gradually returned to normal, and the anemia slowly improved. The child was discharged in apparently good health eight days later.

COMMENT

Although, unfortunately, no inoculation of animals was performed to recover the spirochete, it is felt that clinically this case fulfils many of the criteria of sodoku, or the S. minus type of rat bite fever, so that it could be listed as such rather than the rat bite fever caused by S. moniliformis.

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ARSENICAL TREATMENT FOR PEMPHIGUS

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The treatment for pemphigus may be approached from two viewpoints: (1) the etiologic or rational and (2) the empiric. As the cause of pemphigus is still obscure, with the bacterial, virus and neurogenic factors contending for sole recognition, the effect of any remedial agent can be judged only by clinical results.

The treatment herein described is based on the hypothesis that arsenic, an epidermal stimulant, has proved up to the present to be an acceptable treatment for pemphigus. The failure of many of the arsenicals to be helpful in pemphigus is due, in my opinion, to overstimulation or too intense stimulation. Weakened epithelial cells will respond to mild stimulation rather than overstimulation, just as a tired horse will to gentle urging rather than to driving. A glance at the pathology of pemphigus will prove this point. The pathologic picture of pemphigus is bleb formation–solution of epithelial cells, and if the cells not completely

destroyed are to be given a chance to survive, a minute almost infinitesimal quantum of a stimulating medicament should be applied.

With this concept in mind, two types of arsenical preparations are herein proposed: (1) a small amount of serum containing only a minute amount of arsenic given intravenously (Swift-Ellis treatment) and (2) sulfarsphenamine given intramuscularly. It has a prolonged arsenic effect, almost without reaction and with slow absorption. Normally, a patient is given 0.6 Gm. of neoarsphenamine intravenously, and twenty minutes later 50 cc. of blood is withdrawn. The tube containing the blood is refrigerated, and when the serum has separated it is pipetted off and centrifuged. The serum is now inactivated, and 8 to 12 cc. of this serum is given intravenously. For three to four treatments, such injections are given at four to five day intervals. Thereafter these injections are given every week or ten days. The sulfarsphenamine, in the amount of 0.1 Gm., is given at first about three days after the intravenous injections and thereafter about once every week.

Five patients with toxic pemphigus were treated with this method.

REPORT OF CASES

Case 1.—Mrs. B., white and aged 49, presented a cutaneous eruption of three months' duration. It consisted of blebs involving the greater part of the cutaneous surface, including the axillary and groin areas. The blebs were partly distended and arose from apparently normal skin. There was no sign of healing. The patient was weak and toxic. The diagnosis was pemphigus vulgaris.

Physical examination revealed no definite abnormalities.

Laboratory Studies.—The urine contained albumin and hyaline casts. The blood contained hemoglobin 70 per cent, red blood cells 3,910,000 and leukocytes 11,200, with a normal differential count. Determinations for sugar and urea nitrogen in the blood were normal. The sedimentation rate was 23 mm. per hour. The Wassermann reaction of the blood was negative.

This patient was admitted to the Skin and Cancer Hospital Sept. 5, 1944. She received five injections intravenously (modified Swift-Ellis), 8 to 12 cc. each, and seven intramuscular injections of sulfarsphenamine, 0.1 Gm. each. She was discharged November 26, with lesions healed and feeling well. She reported to me from time to time, and on June 28, 1946, almost two years after her discharge, she was well and free of eruption.

Case 2.—A. C., a white man aged 50, presented a generalized eruption of four weeks' duration. The body was almost completely covered with lesions, and eruptive elements were present on the buccal mucosa. Clinically, the picture was that of pemphigus vegetans. He was admitted to the Skin and Cancer Hospital Nov. 6, 1944.

The physical examination revealed no abnormalities except that the patient was toxic.

Laboratory Studies.—The blood cell count was normal; the urine contained albumin and hyaline casts; the determinations for sugar and urea nitrogen in the blood were normal, and the Wassermann reaction of the blood was negative.

This patient ran a septic temperature for six weeks. He received five injections intravenously of arsphenamized serum (8 to 12 cc. each) and nine intramuscular injections of sulfarsphenamine, 0.1 Gm. each. He was discharged March 18, 1945, with the eruption cleared. He was last seen May 3, 1946, well and without lesions.

Case 3.—M. L., a white woman aged 53, was admitted to the Skin and Cancer Hospital on Jan. 28, 1945, with a generalized eruption of three weeks' duration.

Lesions typical of pemphigus covered almost the entire body; buccal lesions were also present. The diagnosis was pemphigus vegetans. This patient had considerable itching and was toxic on admission.

Physical examination revealed no abnormalities.

Laboratory Studies.—The urine showed a trace of albumin. The blood cell count was hemoglobin 77 per cent, red blood cells 3,880,000 and white blood cells 20,800, with a normal differential count. The determinations of sugar and urea nitrogen in the blood were normal, and the Wassermann reaction of the blood was negative.

This patient received seven injections (modified Swift-Ellis) intravenously (8 to 12 cc. each) and six intramuscular injections of sulfarsphenamine. While healing of the lesions was taking place, there developed a decided drop of hemoglobin to 55 per cent, necessitating three transfusions of 500 cc. each. The hemoglobin gradually increased, and when the patient was discharged it was 80 per cent. She was discharged April 2, free of lesions and feeling well. At the time of writing, July 6, 1946, the patient had remained free of eruption.

CASE 4.—A Negro, aged 60, presented a bullous eruption of several months' duration. The eruption was generalized and typical of pemphigus, with the mucous membranes unaffected. The diagnosis was pemphigus vulgaris. He entered the Skin and Cancer Hospital Oct. 15, 1945.

Physical examination showed the patient to be much overweight and suffering from asthma; otherwise he was apparently normal.

Laboratory Studies.—The urine contained albumin and hyaline casts; the blood was normal except for leukocytosis (15,200).

This patient received eight intravenous injections of arsphenamized serum and fifteen intramuscular injections of sulfarsphenamine (0.1 Gm.). After three months of treatment there developed an inflammatory process of the palms and soles, suggestive of beginning keratosis palmaris et plantaris, as well as patches of vesicular eczema on the arms and legs. With local treatment the vesicular lesions cleared and the keratotic lesions were much improved. At the time of writing, July 6, 1946, the patient is still in the hospital with a few lesions still to be healed, but free of pemphigus eruptions. No new pemphigus lesions had appeared for three months, but some of the old lesions became infected and healed slowly.

CASE 5.—S. M., a white man aged 55, was admitted to the Skin and Cancer Hospital June 7, 1945 with a generalized eruption consisting of blebs, moist scales and denuded areas. Nikolsky's sign was present. Lesions were absent in the mucous membrane. The picture was typical of pemphigus foliaceus.

Physical examination revealed no abnormalities except for the cutaneous lesions.

The skin improved with treatment, but on November 20 pneumonia developed and penicillin was given, which while it controlled the pneumonic process greatly aggravated the pemphigus, and generalized erythema with exfoliation developed. After one month improvement again was apparent. On Jan. 20, 1946, pneumonia again developed, and he was treated with sulfadiazine, with no setback of the eruption. The patient received, in all, thirty-two intramuscular injections of sulfarsphenamine (0.1 Gm. each) and eleven intravenous injections of arsphenamized serum. He finally died from asthenia. Possibly this patient had adrenal cortex insufficiency. Even during his last hours of life his skin remained about normal. Permission for an autopsy could not be obtained.

While at the time of admission the blood and the urine were fairly close to normal, during and after the pneumonia moderate anemia with albumin and hyaline and granular casts developed, which persisted.

It should be stated that in the treatment of these patients with pemphigus various baths were prescribed from time to time, as a measure of cleanliness, and local preparation as the state of the skin demanded. Various vitamins were given, particularly vitamin A and the vitamin B complex group.

It was observed that at times after intravenous medication and also after the administration of sulfarsphenamine a temporary flare-up of the eruption would occur, but this would always subside in a day or two.

COMMENT

Pemphigus, from a practical viewpoint, should be divided into the toxic and nontoxic types. It is the toxic type which calls for all the skill and knowledge dermatologists can muster to combat it. It is my belief that the generalization and widespread character of the eruption, the lack of tendency to heal, secondary pyogenic infection and the general toxic condition of the body are the criteria by which one can recognize the toxic type. The Pels-Macht test serves as a laboratory test to determine toxicity, and the same can be said for the sedimentation rate test.

Arsenic is an epidermal stimulant, both mild and intense in its effect. It can help the weakened epidermal cells, but a vesicular eruption can result from overstimulation (intoxication). Is it not therefore possible, at times when the arsenic effect is overintense and the vitality of the epidermal cells at low ebb, that a pemphigus-like eruption of arsenical origin could appear which could be mistaken for a true pemphigus eruption? It is my belief that this does occur. Therefore, there is need of great care and caution in the use of arsenic in the treatment for pemphigus.

SUMMARY

A new approach in arsenical therapy for pemphigus is proposed, which, in my hands, has proved successful in 4 out of 5 cases, with restoration of the skin to normal and, to date, absence of recurrences. These periods of freedom from eruption have extended from two years to four months, dependent on the date of the discharge of the patients. The treatment consists of administration of minute amounts of arsenic intravenously, with the Swift-Ellis technic, repeated at four to five day intervals for the first three to four treatments and then once weekly. In addition sulfarsphenamine (0.1 Gm.) is given intramuscularly once a week. It is possible that acetylaminohydroxyphenylarsonic acid ("acetarsone") may be incorporated in this treatment with decided benefit.

327 South Sixteenth Street.

CHROMOBLASTOMYCOSIS IN PANAMA

Report of a New Case and a New Clinical Form

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The purpose of this article is to report a new case of chromoblastomycosis, diagnosed in the Hospital Santo Tomas, with what I consider to be a new clinical form of the disease.

From the Department of Medicine, Santo Tomas Hospital.

REPORT OF A CASE

E. H., a white man 30 years of age and born in Corozal (Province of Los Santos), Republic of Panama, where he had lived and worked as a farmer (wearing sandals), was hospitalized for a verrucous type of dermatosis on the anteroexternal aspect of the left leg (fig. 1*A*) of two years' duration. The lesion began as a small nodule and gradually increased in size. It bled easily with minor traumatism and was slightly pruritic and not painful. On removal of the crust from the cutaneous surface which had been traumatized, there was a seropurulent exudate which had a typical odor.

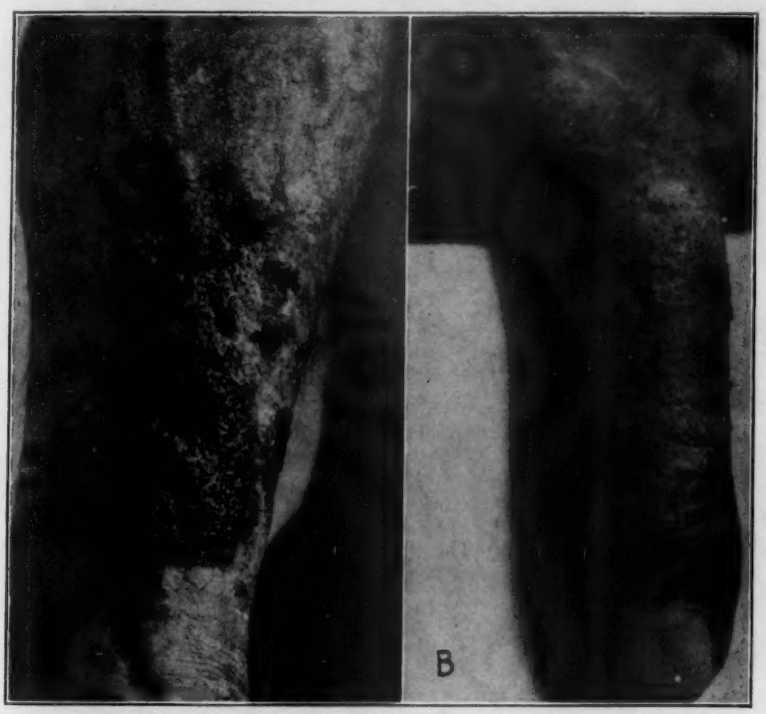

Fig. 1.—*A*, verrucous lesion located on the anteroexternal aspect of the left leg. *B*, eczematoid type of lesion located on the dorsal aspect of the middle finger of the right hand (with sclerotic cells in the scraped material).

The verrucous nodule at the time of my examination measured 16 by 16 cm. in its widest diameters. Around the borders were other nodules of variable size, with the same characteristics as described previously.

The general examination of the skin revealed, however, that the patient had another dermatologic lesion, of one year's duration, which was located on the dorsal aspect of the middle finger of the right hand (fig. 1*B*). The solitary lesion, regardless of its long period of evolution, did not invade the nail, had a sharp raised border, measured 5 by 6 cm. and was pruritic and covered with whitish, greasy scales. There was only occasional and slight bleeding on removal of the scales, leaving a smooth glistening surface, more eczematoid than psoriasiform in appearance.

Finally, around the neck and also, although less pronounced, at the angles of flexion of the extremities (especially in the popliteal fossae) were observed areas of moderate infiltration (fig. 2), well demarcated, causing pruritis and accentuating the natural folds of the skin, without evidence of desquamation, excoriation, vesiculation or formation of verrucae, which the patient stated had developed during the previous month.

The results of the general examination of the patient were essentially negative, with the exception of moderate anemia and severe dental decay with several bad snags.

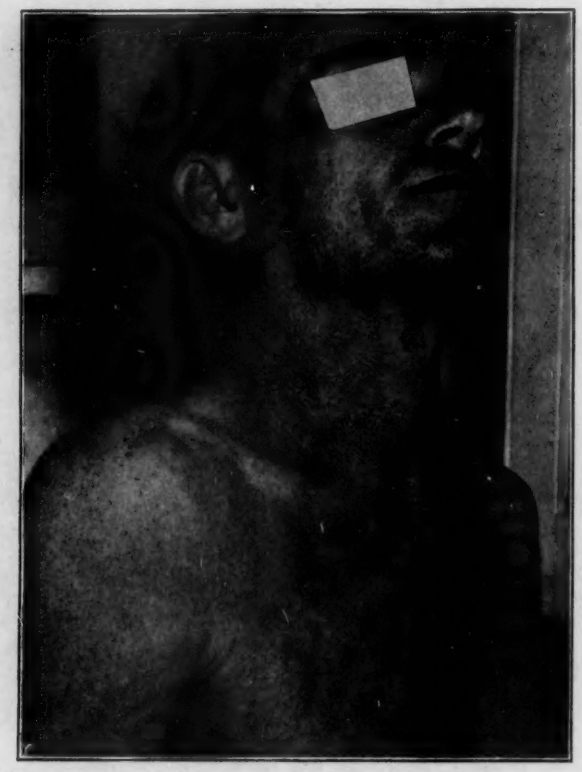

Fig. 2.—"Id" type of dermatosis located around the neck (without sclerotic cells).

The laboratory examination revealed intestinal parasitism (Uncinaria and larvae of Strongyloides organisms). The anemia was observed to be a microcytic hypochromic type with eosinophilia (14 per cent). The Kahn reaction was negative, and Hematozoaria organisms were not demonstrated. The urine was normal. There was no evidence of changes in the bones in roentgenograms of the left leg or of the right hand where the mycotic infections were located.

Examination of the material scraped from the verrucous nodule and from the digital lesion, in the routine method for studying fungi, revealed (in both lesions) characteristic sclerotic cells (fig. 3). Repeated scraping and examination of the skin of the neck and folds of the extremities, in the same manner, revealed no sclerotic cells.

Histologic Examination.—I observed the same type of histologic lesion as I reported previously,[1] with keratinization of the epidermis, acanthosis, zones of necrosis and round cell and polymorphonuclear cell infiltration of the dermis. As many characteristic sclerotic cells were observed in the epidermis as in the dermis, some being intercellular and others (fig. 4) engulfed by giant cells.

Mycologic Examination.—Culture of the strain from the patient, grown on Sabouraud's proof medium at room temperature (28 C. [82.4 F.]), showed dominating forms with the hormodendron characteristics. Few Phialophora and Acrotheca organisms were seen. I classified this strain in the genus *Fonsecaea pedrosoi* Negroni,[2] variety communis Carrión.[3]

Fig. 3.—Sclerotic cells, brown with thick wall and septation (× 1800).

Treatment.—The patient refused to continue his hospitalization for the period of time necessary for treatment, because personal economic circumstances required his attention.

1. Calero M. C.: Chromoblastomycosis: Report of Two New Cases in the Isthmus of Panama, Arch. Dermat. & Syph. **54**:265 (Sept.) 1946.

2. Negroni, P.: Estudio micológico del primer caso argentino de Cromomicosis, Rev. d. Inst. bact. **7**:419 (March) 1936.

3. Carrión, A. L.: Chromoblastomycosis, Mycologia **34**:424 (July-Aug.) 1942

COMMENT

In the 3 heretofore reported cases from the Isthmus of Panama,[4] the diagnosed clinical type of the disease has been described as verrucous.

It is interesting, nevertheless, to consider a new clinical type of the disease, different from the forms reported and which Pardo-Castelló and his co-workers[5] described as verrucous, tuberculoid, syphiloid, psoriasiform and cicatricial-elephantiasic. I refer to the second type of lesion of the patient (fig. 1*B*), which appeared eczematoid in nature. I made the diagnosis by the type of the scale, the unique location of the lesion, its slight tendency to bleed on removal of the

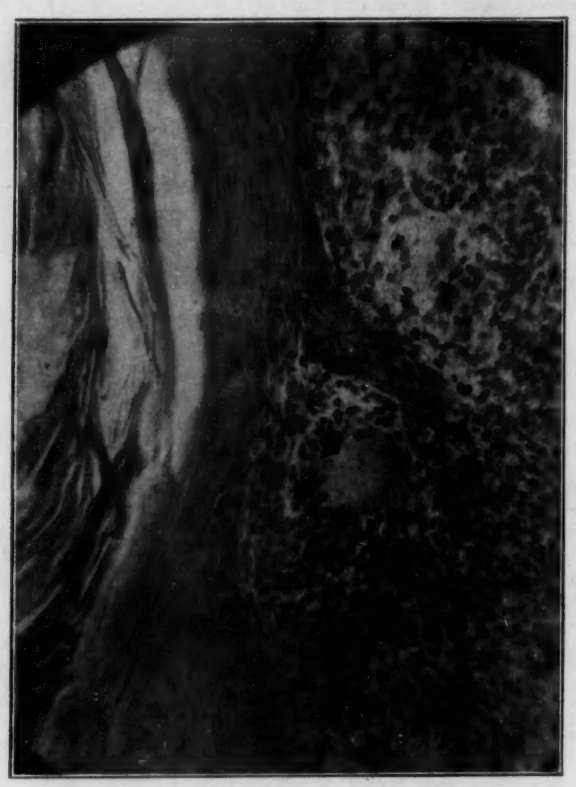

Fig. 4.—Giant cell with two engulfed sclerotic cells, showing the decided infiltration of the dermis (× 460).

scale, the fact that the finger nail played no part in the evolution of the neighboring lesion, the decided eosinophilia and the associated "id" type of dermatosis (fig. 2), probably due to the same fungus of chromoblastomycosis that was present.

4. Calero.[1] Snow, J. S.; Wedding, E. S., and Tomlinson, W. J.: Chromoblastomycosis: Report of the First Case Observed in the Canal Zone, Arch. Dermat. & Syph. **51**:90 (Feb.) 1945.

5. Pardo-Castelló, V.; León, E., and Trespalacios, F.: Chromoblastomycosis in Cuba, Arch. Dermat. & Syph. **45**:19 (Jan.) 1942.

The case herein reported is important because the patient presented three different types of cutaneous lesion: verrucous, eczematous (with sclerotic cells in the scraped material) and "id" (without sclerotic cells).

SUMMARY

A new case of chromoblastomycosis is reported from the Isthmus of Panama, of what I consider to be a new clinical type of the disease, eczematoid in appearance, associated with the verrucous type of lesion.

The mycologic examination revealed that the pathogenic fungus was Fonsecaea pedrosoi Negroni,[2] variety communis Carrión.[3]

Apartado 957.

HESPERIDIN AND HESPERIDIN WITH ASCORBIC ACID IN TREATMENT OF PSORIASIS

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Psoriasis is one of the oldest known cutaneous diseases, the cause of which has not been determined. The disease is no respecter of sex, age or social position and is apparently not occupational. Psoriasis seems to by-pass dark-skinned races, as it is infrequently observed in them.

A relationship has been shown between psoriasis and injury and between injury and increases in capillary fragility according to Goldfarb [1] who quoted Kromayer's [2] conclusion that "the slight increase in the permeability of the capillaries, incident to their dilatation, produces a hyperalimentation of the epidermis which in turn results in the pathologically altered cornification of psoriasis."

Improvement in 65 per cent and 86 per cent of patients with psoriasis treated with citrin lemonade was reported by Goldfarb.[3] The improvement noted consisted of diminution of the infiltration of the lesions and a lessening of scaling.

Citrin is the original name used to describe vitamin P isolated from citrus fruits. The active substance in citrin has been identified as hesperidin,[4] a vitamin-like substance of flavone nature, which serves to control the tonicity of capillaries.[5] It is

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1. Goldfarb, A. E.: Causes of Psoriasis, New York State J. Med. **44**:1111-1114 (May 15) 1944.

2. Kromayer, E.: Zur pathologischen Anatomie der Psoriasis nebst einigen Bemerkungen über den normalen Verhornungsprocess und die Structur der Stachelzelle, Arch. f. Dermat. u. Syph. **22**:557 (Oct.) 1890.

3. Footnote.[1] Goldfarb, A. E.: The Treatment of Psoriasis by the So-Called Vitamin P, M. World **63**:29 (Jan.) 1945; Treatment of Psoriasis with Lemon Citrin (Vitamin P), Citrin Lemonade and Ascorbic Acid, Arch. Dermat. & Syph. **43**:536 (March) 1941.

4. (*a*) Bruckner, V., and Szent-Györgyi, A.: Chemical Nature of Citrin, Nature, London **138**:1057 (Dec. 19) 1936. (*b*) Ruszynäk, I., and Szent-Györgyi, A.: Vitamin P: Flavonals as Vitamins, ibid. **138**:27 (July 4) 1936.

5. (*a*) Scarborough, H., and Stewart, C. P.: Effect of Hesperidin (Vitamin P) on Capillary Fragility, Lancet **2**:610 (Sept. 10) 1938, (*b*) Lindheimer, G. T.:

(*Footnote continued on next page*)

believed that hesperidin is a precursor of vitamin P, which is broken down in the digestive system to form this vitamin.

It has been assumed that vitamin C subnutrition was a factor in capillary fragility, but a number of investigators [6] have shown that capillary resistance and vitamin C avitaminosis were not necessarily related.

Experimental and clinical work [7] has been carried out on the basis of the ability of hesperidin to decrease capillary permeability and increase capillary resistance. The clinical evidence would seem to indicate the effectiveness of hesperidin in correcting capillary fragility.

Various chemical and clinical observations [4b] have led to the assumption that ascorbic acid is accompanied in the cell with a substance similar in importance and activity. The natural occurrence of hesperidin and ascorbic acid together and the clinically demonstrated supplementary nature of their actions would tend to indicate their efficacy in capillary fragility.

Assuming the relationship between psoriasis, injury and capillary fragility as a possible causative factor and being impressed with the clinical reports on the efficacy of hesperidin alone and hesperidin and ascorbic acid in combination in correcting capillary fragility, it was decided to try these substances in several groups of patients with psoriasis.

Patients for this study were treated in the private practice of one of us (M. L. N.) and at the Temple University Skin Clinic. All other types of treatment were discontinued, the patients being given only hesperidin, 100 mg. tablets,[8] or tablets of hesperidin, 50 mg., combined with ascorbic acid, 50 mg.,[8] or ascorbic acid tablets, 100 mg. each.

Warter and his associates [6e] reported on the efficacy of preparations having identical composition as the aforementioned preparations as useful agents in correcting capillary fragility as observed in patients with rheumatoid arthritis. Similar observations are being reported by other investigators.

Thorough medical studies were made in all the patients, and they all had previously received various types of treatment. We have been greatly discouraged by

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Hinman, W. F., and Halliday, E. G.: Functions and Occurrence of Citrin (Vitamin P), J. Am. Dietet. A. **18**:503 (Aug.) 1942. (*c*) Griffith, J. Q., and Lindauer, M. A.: Increased Capillary Fragility in Hypertension: Incidence, Complications and Treatment, Am. Heart J. **28**:758 (Dec.) 1944.

6. (*a*) Greene, D.: Evaluation of Capillary Resistance Test in Diagnosis of Subclinical Scurvy, J. A. M. A. **103**:4 (July 7) 1934. (*b*) Molitch, M.: Subclinical Scurvy in Children: Application of Capillary Resistance Test, J. Lab. & Clin. Med. **21**:43 (Oct.) 1935. (*c*) Weld, C. B.: Capillary Resistance and Its Relation to Vitamin C and D, J. Pediat. **9**:226 (Aug.) 1936. (*d*) Göethlin, G. F.: When Is Capillary Fragility a Sign of Subnormal Supply of Vitamin C in Man? abstracted, Lancet **2**:703 (Sept. 18) 1937. (*e*) Warter, P. J.; Drezner, H. L., and Horoschak, S.: Effects of Hesperidin and Ascorbic Acid on Capillary Fragility in Rheumatoid Arthritis, New Jersey M. J. **43**:228 (June) 1946.

7. Scarborough and Stewart.[5a] Warter, Drezner and Horoschak.[6e] Armentano, L.; Bentsath, A.; Beres, T.; Ruszynäk, I., and Szent-Györgyi, A.: The Effect of Substances of the Flavone Group on Capillary Permeability. Vitamin P, Deutsche med. Wchnschr. **62**:1326 (Aug.) 1936. Rinehart, J. F.: The Treatment of Rheumatic Fever with Crude Hesperidin (Vitamin P), California Health **1**:163 (May 31) 1944.

8. The tablets were supplied by the Medical Research Department of the National Drug Company, Philadelphia.

systemic medication. One of us (M. L. N.) observed that sodium salicylate given intravenously, vitamin D administered in large doses and autohemotherapy were of uncertain value. Soybean preparations were ineffectual. We have been relying almost exclusively on external treatment for any benefit that may be derived in this disease in a large percentage of our patients. We are using chrysarobin or its derivatives, salicylic acid and tar preparations for external treatment and are under the impression that these are the most effective in the order named.

REPORT OF TREATMENT

GROUP 1.—Twenty patients with definitely diagnosed psoriasis of eight years' average duration were given hesperidin, 100 mg. four times daily. Since none of the patients showed any improvement within four weeks, it was decided to increase the dose to 600 mg. daily. With this dose, slight improvement was noted in 1 patient after two weeks. Treatment continued for four months, with the results as recorded in the table

GROUP 2.—Twenty patients were given hesperidin, 50 mg., combined with ascorbic acid, 50 mg., beginning with four tablets a day. Improvement was manifested in 1 patient after the third week. The tablets were increased to six a day. Three weeks following the increase, 2 patients manifested improvement. Results are recorded in the table.

*Summary of Treatment and Results**

Group	Medicament	Number of Patients	Patients Improved	Patients with No Change	Patients Who Became Worse
1	Hesperidin	20	1	12	7
2	Hesperidin and ascorbic acid	20	3	12	5
3	Ascorbic acid	10	1	4	5
4	Placebo	10	2	3	5

* All patients were under treatment and observation for at least four months.

GROUP 3.—Ten patients were given ascorbic acid, 100 mg. tablets, with an initial dose of 400 mg. daily. At the end of the first week, the dose was increased to 600 mg., and this dose was continued for four months. Results are recorded in the table.

GROUP 4.—Ten patients were given placebo tablets, with no other type of treatment.

COMMENT

The administration of hesperidin or hesperidin combined with ascorbic acid may apparently decrease capillary permeability and increase capillary resistance, but our clinical observations would seem to indicate that these vitamins or vitamin-like substances do not have sufficient beneficial effects on the psoriatic lesions to recommend them for treatment.

We have discovered no remedy which can be internally administered to be effective in the treatment of psoriasis. We rely on external treatment for any relief that may be obtained.

Our observations are contrary to those of Goldfarb, who, of course, used extemporaneously prepared citrin lemonade. It remains to be determined whether the latter preparation contains factors not present in highly purified products comparable to those we employed in this investigation.

500 Central Medical Building.

PHTHIRUS PUBIS INFESTATION OF THE SCALP AND CILIA IN YOUNG CHILDREN

Report of Five Additional Cases

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Infestation of the scalp with Phthirus pubis is an uncommon occurrence. The relatively few reports in the literature have been of cases in children. With the apparent increase in recent years of parasitic infections of the skin, it is evident that infestation of the scalp with P. pubis is also increasing. Since the report in 1941,[1] 5 additional cases have been seen. In each case the parasites were identified. Moreover, in each case there was associated involvement of the cilia. The majority of the cases have been referred by ophthalmologists who are now aware of this association in children. If the infestation of the scalp is mild and the mother is not observant, there is apt to be little complaint on the part of the child. Even in the cases of severest disease the extent and degree of infestation of the scalp are much less than with the infestation in pediculosis capitis. The age of the children varied from 19 months to 7 years. Including the previous report, to date 4 cases have been observed in girls and 2 in boys. All were white children. Four of the families involved were families of physicians. In only 1 case was a source of infection found, and the father had been suspected. In none of the physicians' families was it possible, even with detailed tracing, to find the source. In the 6 cases seen, in only one instance was more than 1 child in the family involved. One girl, 7 years of age, had extensive involvement of almost the entire scalp, without, however, eczematoid dermatitis or adenitis. In the majority of the instances the infestation was limited to the hair, with that about the forehead, usually the commonest site, and next, that about the ears. Parasites were few, and also the number of nits were few. The treatment for the infestation of the scalp is the usual treatment for pediculosis in that area. Benzyl benzoate and DDT (dichlorodiphenyltrichloroethane) mixtures have been used recently. The infestation of the cilia is not easy to control even with the use of ointments of mercury. With the difficulty of restraining the child, ophthalmologists may often resort to manual removal, frequently under a general anesthetic. The involvement of both the scalp and the cilia must be cleared. Otherwise there will be recurrence. No investigative studies have been done to determine the reasons for limitation of such type of infestation to the scalp areas and cilia and to young children.

CONCLUSIONS

Involvement of the scalp should be suspected in children with infestation of the cilia with Phthirus pubis. The involvement of the scalp is apt to be mild, usually about the hair adjacent to the forehead, and is often without subjective complaints on the part of the child.

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati.

1. Goldman, L., and Friedman, L. S.: Infestation of the Scalp and Cilia with Phthirus Pubis in a Nineteen Month Old Baby, Am. J. Dis. Child. **61**:344 (Feb.) 1941.

THIOGLYCOLLATE COLD WAVE PROCESS

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A great variety of substances entering into the manufacture of cosmetics have caused allergic reactions in hypersensitive persons. The essential oils, perfumes and orris root are the most frequent offenders. Soaps containing these constituents and even pure high grade soaps may cause dermatitis. Jordan, Dolce and Osborne [1] stated that eczematous dermatitis of the hands of housewives is one of the commonest and most refractory diseases for which dermatologists are consulted. They found 239 persons during a four year period in whom soap caused dermatitis on the hands, with and without involvement of other parts of the body. We have observed that in patch tests with medicated soap 15 per cent of the controls were allergic to a pure white soap. Vaughan [2] observed in routine patch tests with soap solutions that 5 to 10 per cent of persons tested reacted to one or another of the common brands, though persons who reacted to soap usually do not react to all brands. Biederman [3] reported on 19 patients who had allergic complaints as the result of using a shampoo. These patients were undoubtedly allergic to a particular popular brand of shampoo, as evidenced by the same reactions following repeated contact. Even simple substances, such as wool fat, have caused contact dermatitis (Sulzberger and Morse [4]). In view of this, it would be certain that the application of many chemical substances, such as the ammonium salts of thioglycollic acid, could cause a reaction in hypersensitive persons, or if allowed to remain on the skin for long periods of time they might cause untoward reactions. With this in mind, commercial preparations were subjected to toxicologic and chemical tests.

In 1893, Smith [5] fed dogs (weighing 25 pounds [11.3 Kg.]) 2 Gm. of ammonium thioglycollate for two days, without any toxic symptoms, but larger doses (5. Gm.) produced vomiting. When the drug was tolerated, complete oxidation of the drug took place in the dogs. In 1924, Hill and Lewis,[6] in the course of experiments with compounds of that type, noted that thioglycollate in the form of the sodium or potassium salts was somewhat toxic to rabbits. A dose of approximately 600 mg. caused death, while a dose of 300 mg. caused noticeable malaise. The rabbits weighed approximately 2 Kg. Most of the other work done with thioglycollic acid and other sulfhydryl compounds has been concerned with the stimulation of the growth of granulation tissue and with healing

1. Jordan, J. W.; Dolce, F. A., and Osborne, E. D.: Dermatitis of the Hands in Housewives, J. A. M. A. **115**:1001 (Sept. 21) 1940.

2. Vaughan, W. T.: Practice of Allergy, St. Louis, C. V. Mosby Company, 1939.

3. Biederman, J. B.: New England J. Med. **217**:1088, 1937.

4. Sulzberger, M. B., and Morse, J. L.: Hypersensitiveness to Wool Fat, J. A. M. A. **96**:2099 (June 20) 1931.

5. Smith, W. J.: Ztschr. f. physiol. Chem. **17**:459, 1893.

6. Hill, R. M., and Lewis, H. B.: J. Biol Chem. **59**:557, 1924.

of wounds (Hammett,[7] Reimann,[8] and Brunsting and Simonsen[9]). Reimann[10] observed that 4 per cent of the subjects were sensitive to sulfhydryl compounds, while Sutton[11] observed a sensitivity in only 1.9 per cent of the subjects tested. Pak and Read[12] observed that thioglycollate and antimony thioglycollamide were less toxic than antimony potassium tartrate in subcutaneous and intravenous injections. Tyler[13] reached the conclusion that the use of thioglycollate dilute wave solution over a ten minute period could probably be considered safe for commercial use, while it has toxic properties and is even lethal in large quantities. Cotter[14] recently reported untoward results of thioglycollic acid poisoning in a cold wave process. The cases reported by him could have been from several other causes, not related to the use of a cold wave solution. The pure acid is never used, even as a base, and the weaker acids (such as 60 per cent acids) are always neutralized by some alkaline substance, such as ammonia, before leaving the manufacturer. McCord[15] has criticized the report of Cotter as containing misstatements and contradictions. We do not agree with McCord that there is no primary cutaneous irritation from thioglycollic acid preparations at levels below 8 per cent, as will be noted in the following report. We agree with him that there is little evidence of sensitization and allergic response with properly prepared materials.

A number of experiments with animals were made for the purpose of determining the action of the solution (containing 6.5 per cent ammonium thioglycollate) when applied topically to normal and to abraded tissue and, further, to determine the potential toxicity of the solution on the assumption of possible absorption through the skin. Toxicologic studies were made on 42 white rats and 12 guinea pigs.

The method of procedure was as follows: 6.5 per cent ammonium thioglycollate solution was applied to the back of the white rats with normal skin and allowed to remain thereon for one hour (experiment 1 was an exception). These animals were kept in cages until the following morning, when this same procedure was repeated. The solution was applied daily, six days a week, for a period of about three months and over an area 1½ by 2 inches (about 3.8 by 5 cm.). In 12 of these animals (rats) the skin was purposely scarified and the solution was applied for one week, using the same method as in experiment 2. It was observed that there was a severe local irritation, and the test was discontinued after a seven day period. The skin on these animals was allowed to heal, after which the animals were normal. This would indicate that there was not enough absorption through

7. Hammett, F. S.: Protoplasma **7**:297, 1929.

8. Reimann, S. P.: Use and Reasons for the Use of Thiocresol to Stimulate Wound Healing, J. A. M. A. **94**:1369 (May 3) 1930.

9. Brunsting, L. A., and Simonsen, D. G.: Cutaneous Ulcers Treated by the Sulphydryl Containing Amino-acid Cysteine, J. A. M. A. **101**:1937 (Dec. 16) 1933.

10. Reimann, S. P.: Am. J. Clin. Path. **3**:167, 1933.

11. Sutton, L. E.: Thioglycerol, J. A. M. A. **104**:2168 (June 15) 1935.

12. Pak, C., and Read, B. E.: Chinese J. Physiol. **14**:375, 1939.

13. Tyler, C. A.: Consumers Research Bull. **14**:232, 1944.

14. Cotter, L. H.: Thioglycolic Acid Poisoning in Connection with the Cold Wave Process, J. A. M. A. **131**:592 (June 15) 1946.

15. McCord, C. P.: Toxicity of Thioglycolic Acid Used in Cold Permanent Wave Process, J. A. M. A. **131**:776 (Jan. 9) 1946.

the abraded skin to cause a general reaction. At the end of the experimental period these animals were observed to be in good condition, and 1 had a litter of healthy young rats. One rat in the other group with normal skin also had a litter of healthy young rats at the conclusion of the experiment.

The same method of application of the solution was used on 6 guinea pigs.

Examinations of the blood of 6 rats picked from the 42 which were used in the research, during the period of the tests and two weeks after cessation of the experiment, did not reveal any alterations in the blood picture, which indicates absorption was never sufficient to cause toxic reactions in the hemopoietic system.

Dermatologic studies were made on 154 human subjects, 76 with normal skin and 78 who had had various types of cutaneous disease. No dermatitis or irritation resulted in any of them.

EXPERIMENTS WITH ANIMALS

EXPERIMENT 1.—Twelve white rats were used in this experiment, male and female, of common stock and of nearly the same age. These animals had been raised in our laboratory. They were healthy, with hair and skin of normal appearance. Cold wave solution (containing 6.5 per cent ammonium thioglycollate) was applied on the back of these animals, allowed to remain until the following day, then completely washed off and a new application of the solution applied and allowed to remain on the back of these rats for the same length of time. This procedure was followed for ten days. On the second day following the first application of the solution, a redness was noted on the skin of the animals. After several days, the hair began to fall out and the animals lost weight.

When this method of application was changed to a less drastic one, as used in experiment 2, the inflammation of the skin subsided, the skin returned to normal and the hair began to grow.

EXPERIMENT 2.—In this experiment, 12 white rats were used. Each animal was healthy, and the hair and skin were normal in appearance. The 6.5 per cent ammonium thioglycollate solution was applied on the back of these animals, allowed to remain for sixty minutes and then completely washed off. No further applications were made that day. On the following morning, at 8:30, another application of the solution was made, allowed to remain for sixty minutes and then washed off. The method of application of the solution for sixty minutes simulated the actual process used in the cold wave process in human subjects. The skin was not irritated in any of the animals during the entire experiment, and there was no loss of hair.

In the usual method in the beauty shop the hair is cut, shaped and shampooed. After it is dried with a towel or electric dryer, the hair is blocked. Approximately thirty-five to forty-five curls are made, according to the size of the head and the amount of hair. The cold wave solution (thioglycollate) is poured into a clean shallow dish. No metal is allowed to come in contact with the solution, as staining of the hands or hair would result, which is difficult to remove. The waving solution is applied with a brush or sponge, after winding the hair on rods, never using an excess of waving solution that might run onto the scalp. The operator is advised to wear rubber gloves while applying the cold wave solution and to keep the solution on the hair ¼ inch (about 1.27 cm.) away from the scalp. A test curl is made to approximate the time for allowing the waving solution to remain on the hair. The hair is covered with a paper hood, and a plastic processing cap is applied over the paper for forty to sixty minutes, depending on the time determined by the test curl. Some operators use only a towel over the curls. After forty minutes the waving solution is neutralized, while the curls are

still in place, with a solution of potassium bromate, hydrogen peroxide or dilute acetic acid. A shampoo is usually given at this point to remove the disagreeable sour odor of the thioglycollate. The hair is then set, dried under the dryer and combed out and a lacquer is applied. We have observed dermatitis caused by a synthetic lacquer in 20 persons.

EXPERIMENT 3.—In another experiment, 12 white rats were used. The skin of the back of these animals was purposely abraded in an area 1½ by 2 inches (about 3.8 by 5 cm.), and the 6.5 per cent ammonium thioglycollate solution was applied, allowed to remain for sixty minutes and then washed off completely. When this application of the solution was made on the abraded skin of the animals, they were visibly irritated and daily became more difficult to manage. This test was discontinued after seven days. The abraded skin then healed within a week, with no further evidence of injury.

EXPERIMENT 4.—Six guinea pigs were used in this experiment. A 6.5 per cent ammonium thioglycollate solution was applied to an area 2 by 2 inches (about 5 by 5 cm.) on the back. This application of solution was made once a day, six days a week, for one month. During the experiment, twenty-eight applications were made, and at the end of the period no irritation of the skin was noted and no depilatory action resulted. The skin and the hair of the animals remained healthy in appearance.

The examination of the blood of these animals revealed that the red cell count, the amount of hemoglobin in grams per hundred cubic centimeters of blood, the white cell count and the differential count, during the applications of the solutions and two weeks after cessation of the experiment, were unaltered, which indicates absorption was never sufficient to cause toxic reaction in the hemopoietic system.

The dermatologic research with the ammonium thioglycollate solution was made in 154 human subjects, ranging in ages from 16 to 77 years, inclusive. Seventy-six subjects had normal skin and 78 had various types of cutaneous diseases.

The procedure of this research was as follows: The subjects applied the solution on the skin of the arm and at the hairline of the scalp, allowing it to remain for forty minutes to one hour, and then it was washed off with plain water. The applications were made daily, six days a week, for a period of two months. After this time there was no evidence of dermatitis on either the normal skin or on previously diseased skin.

The types and incidence of previous cutaneous diseases were as follows: seborrheic dermatitis 10, eczema 16, acne vulgaris 7, ringworm 5, pityriasis rosea 6, lichen planus 2, psoriasis 5, occupational dermatitis 1, vascular nevus 1, melanoma 1, syphilis 2, streptococcic infection of the feet 2, folliculitis 6, lupus erythematosus 1, stasis ulcer 2, contact dermatitis 2, toxic dermatitis 4, stasis dermatitis 1, tuberculid (acnitis) 1, infectious eczematoid dermatitis 2 and allergic eczema 1.

CONCLUSIONS

From the results of dermatologic studies on 154 human subjects and the toxicologic studies on white rats and guinea pigs, we have concluded that the cold wave solution containing 6.5 per cent ammonium thioglycollate is nontoxic when applied in the manner described in experiment 2. This opinion conforms with the results of millions of tests on human subjects that have been made by beauticians in the process of giving cold waves. Care should be taken when giving a cold wave, and only licensed and experienced operators should handle these solutions.

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CONCEALMENT OF CUTANEOUS BLEMISHES

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The use of lotions and ointments for the protection of the skin and the disguise of defects is widespread. Sensitization to ingredients of the preparations sold for these purposes occurs not infrequently. For such cases I have used the titanium cuticolor paste suggested by Fantus and Dyniewicz.[1] Because of its simple construction there should be relatively little danger of its causing sensitization. The chief likelihood of such action would seem to lie in the use of perfume. If sensitization to perfume should occur, change of perfume or its omission altogether would be easy.

The important ingredient of this paste is titanium dioxide, which in covering power surpasses zinc oxide. The mixture recommended is: red ferric oxide 6.0, yellow ferric oxide 8.0 and titanium dioxide 86.0 The proportion of red and yellow oxides may have to be changed to obtain the shade desired, and it may be necessary to add some darker pigment, such as burnt umber or blood charcoal. Fantus and Dyniewicz suggested the use of a brown powder of the following construction: red ferric oxide 20.0, yellow ferric oxide 4.0, blood charcoal 14.0 and zinc oxide, 62.0. For concealment titanium dioxide should be substituted for the zinc oxide.

The base is a bentonite jelly, made by adding 10 Gm. of sifted bentonite to 75 cc. of stronger rose water, to which has been added 0.5 cc. of liquefied phenol. This is allowed to stand until a jelly forms and then is slowly added with trituration to 15 Gm. of the titanium dioxide cuticolor powder to make a smooth paste. An extremely thin coating of this preparation is sufficient for protection of the skin from light or for the concealment of blemishes. In time the paste will harden from loss of water, but a moistened finger rubbed over its surface will obtain enough for use. It has given satisfaction to many patients.

1. Fantus, B., and Dyniewicz, H. A.: Cuticolor Preparations, J. Am. Pharm. A. **27**:878, 1938.

News and Comment

GENERAL NEWS

Syphilis Study Section of the National Institute of Health.—The Syphilis Study Section of the National Institute of Health, a group of consultants organized for the purpose of promoting research in the field of venereal diseases, announces a symposium, "Recent Advances in the Study of Venereal Diseases," to be held in the Commerce Building, Washington, D. C., on April 8 and 9, 1948.

All interested persons are invited to attend this meeting. Copies of the program will be sent at a later date on request.

All inquiries should be addressed to Dr. Frank W. Reynolds, Executive Assistant, Syphilis Study Section, Division of Research Grants and Fellowships, National Institute of Health, Bethesda 14, Md.

Book Reviews

Dermatologic Clues to Internal Disease. By Howard T. Behrman, M.D. Price, $5. Pp. 165, with 118 illustrations. New York: Grune & Stratton, Inc., 1947.

As indicated in the preface, there is a need for correlating the cutaneous manifestations associated with systemic diseases. The author has undertaken to present, in compendium form, diseases exhibiting this relationship. The commoner dermatoses as well as the exanthemas are not included. Diseases are arranged in alphabetic order, and usually only the salient clinical features are included in the descriptions. Because the author has chosen to present only the "dermatologic clues to internal diseases," he has omitted discussion of controversial issues, therapeutics and histopathology. Longer discussions of some of the more unusual diseases are given, while in other instances brief descriptions are given of the commoner diseases. No mention is made of some disorders, including eosinophilic granuloma, Letterer-Siwe disease, Reiter's disease and metastatic carcinoma

Except for a list of some standard books on dermatology, no specific references to any subject are given. The illustrations are numerous and fairly good reproductions. The quality of the printing and paper is good. No index is included, because of the alphabetic listing of diseases, although there are cross references.

The author, a well qualified dermatologist, has condensed a great amount of material into a small book. It may be useful as a diagnostic aid in obtaining the highlights of these cutaneous-internal disease syndromes. Because of the brevity of the descriptions and lack of other items previously mentioned, dermatologists will probably prefer a more inclusive book.